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Hypertension and Device-Based Therapies for Resistant Hypertension: An Up-to-Date Review

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Abstract

Hypertension poses a global health threat, affecting over one billion individuals and leading to severe cardiovascular complications. Evolving guidelines redefine hypertension criteria, emphasizing individualized treatment goals. Resistant hypertension (RH) and refractory hypertension present significant management challenges, often resulting in adverse cardiovascular outcomes. Device-based therapies have emerged as promising interventions for poorly controlled hypertension, including renal denervation, baroreflex amplification, arteriovenous malformation, pacemaker-based cardiac neuromodulation, electro-acupuncture, and deep brain stimulation. These therapies target various physiological mechanisms to reduce blood pressure and improve patient outcomes.

This article reviews device-based therapies, focusing on catheter-based renal denervation (RDN), baroreflex amplification, arteriovenous malformation, carotid body ablation, pacemaker-based cardiac neuromodulation, electro-acupuncture, and deep brain stimulation. RDN, comprising 70% of RH therapy, includes catheter-based and non-invasive options. Baroreflex amplification utilizes peripheral neuromodulation, while arteriovenous malformation leverages AV anastomosis. Carotid body ablation modulates chemoreceptors, and pacemaker-based neuromodulation adjusts atrioventricular intervals. Electro-acupuncture demonstrates potential, and deep brain stimulation offers central nervous system intervention. Ultrasound and radiofrequency renal denervation have gained FDA approval.

While these approaches show potential, they face challenges related to efficacy, safety, cost, regulatory approval, and patient selection. Addressing these challenges through ongoing research, technological advancements, and clinical implementation is crucial for the successful integration of device-based therapies in hypertension management. Continued innovation and collaboration in this field have the potential to transform the landscape of hypertension treatment and improve patient care.

Categories: Internal Medicine, Cardiology, Medical Physics
Keywords: cvd: cardiovascular disease, renal denervation therapy, device-based therapy, treatment-resistant hypertension, resistant hypertension

Introduction And Background

Hypertension remains a critical global health concern with implications for morbidity and mortality. According to the World Health Organization (WHO), the burden of untreated hypertension is on the rise, affecting over one billion individuals worldwide and leading to potentially life-threatening cardiovascular complications [1, 2]. This escalating crisis has prompted ongoing developments in treatment strategies, particularly focusing on poorly controlled hypertension. Hypertension remains a critical global health concern with implications for morbidity and mortality. According to the World Health Organization (WHO), the burden of untreated hypertension is on the rise, affecting over one billion individuals worldwide and leading to potentially life-threatening cardiovascular complications [1, 2]. This escalating crisis has prompted ongoing developments in treatment strategies, particularly focusing on poorly controlled hypertension.

The 2017 guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) redefine hypertension as an elevated systolic blood pressure (SBP) of 130mmHg or higher or diastolic blood pressure (DBP) of 80mmHg or higher. This is a more stringent criterion compared to the 2003 guidelines, resulting in an increased overall prevalence of hypertension from approximately 32% to 47% [3, 4]. Individualized treatment goals are emphasized, considering various co-morbidities and tailoring blood pressure targets to the patient's characteristics, preferences, and tolerance. For instance, specific goals are outlined for patients with cardiovascular disease, chronic kidney disease (CKD), and diabetes, reflecting recommendations from the 2021 Kidney Disease Improving Global Outcomes guidelines and the American Diabetes Association [5-7].

The ACC-AHA defines Resistant Hypertension (RH) as poorly controlled blood pressure despite the patient receiving at least three medications with different mechanisms of action, even at maximally tolerated doses

[8]. RH is also categorized as controlled blood pressure on at least four medications with different mechanisms of action. The term "pseudo-resistant hypertension" is introduced to describe poorly controlled blood pressure resulting from poor measurement technique, medication non-compliance, or white coat hypertension [8].

Determining the prevalence of resistant hypertension is challenging due to the necessity to rule out pseudo-resistant hypertension. However, estimates from the National Health and Nutrition Examination Survey (NHANES) suggest a prevalence of approximately 12.8% in the general population, using a cutoff of BP >/= 140/90mmHg, and 40.4% in chronic kidney disease [9, 10]. Anticipated factors contributing to an increase in this percentage include an aging population, rising obesity rates, and sedentary lifestyles.

RH is associated with adverse outcomes, including kidney failure, cardiovascular morbidity, and death [11-13]. A recent study involving 10,001 patients with apparent treatment-resistant hypertension revealed a 64% higher incidence of composite cardiovascular complications, such as fatal coronary heart disease, nonfatal myocardial infarction, cardiac arrest, and cerebrovascular accidents [13]. Confirmation of true RH necessitates optimizing the drug regimen following recommendations from the European Society of Cardiology (ESC) and AHA, incorporating lifestyle modifications and meticulous drug management to enhance blood pressure control [14]. Persistent poor blood pressure control prompts the search for secondary causes of hypertension, and interventional procedures become a consideration.

Refractory Hypertension, as defined by the AHA, denotes severe uncontrolled hypertension despite being on five antihypertensive medications from different classes, including mineralocorticoids and thiazide-diuretics [15]. This has spurred the resurgence of interest in device-based therapies, seen as an adjunct to medical therapy. The revitalization of these therapies addresses the need for better hypertension control, particularly in cases of non-adherence to drugs, emphasizing the inhibition of the renin-angiotensin-aldosterone system. After extensive experimental and clinical research in the past two decades, the scientific community has gained a better understanding of the pathophysiology responsible for reducing blood pressure. As of November 2023, two procedural options for treating resistant/refractory hypertension, namely Ultrasound Renal Denervation and Radiofrequency Renal Denervation, have received FDA approval.

This article provides an in-depth and up-to-date review of device-based therapies for resistant hypertension, integrating critical insights from guidelines, studies, and developments in the field.

Review

Device-Based Therapies

1. Renal Denervation (RDN)

Renal Denervation (RDN) is currently the most developed and established therapy for resistant hypertension (RH). Accounting for nearly 70% of RH therapy coverage, more than ten RDN systems are clinically approved for use [16]. Despite being device-based, RDN is not a permanent implant but rather requires only a single surgical intervention.

Pathophysiology of RDN

The efficacy of RDN revolves around the modulation of renal nerves, which play a critical role in kidney function and blood pressure (BP) control. These nerves, particularly the efferent nerves, significantly influence renin release, sodium retention, vasoconstriction, and overall BP regulation [17]. This understanding has driven extensive human and animal trials to assess the safety and effectiveness of RDN.

Clinical Trials Overview

SYMPLICITY Trials

The SYMPLICITY HTN-1 and SYMPLICITY HTN-2 trials, initiated in 2009, were the first to demonstrate promising results in BP control for patients with RH. However, the subsequent SYMPLICITY HTN-3 sham-controlled trial yielded less favorable results, showing no significant superiority of RDN over the sham procedure [18, 19, 20]. These outcomes prompted the development of the DENER HTN trial, which achieved positive results by addressing issues related to patient selection and procedural execution that were identified as potential causes for the SYMPLICITY HTN-3 trial's failure [21, 22].

SPYRAL HTN and RADIANCE-HTN Trials

The SPYRAL HTN and RADIANCE-HTN trials focused on multi-electrode radiofrequency (RF) denervation and ultrasound (US) denervation, respectively. Both trials demonstrated the superiority of these methods over sham procedures [23-27]. Additionally, research into alcohol-mediated denervation and cryo-RDN is gaining momentum, showing promising future applications for these techniques [28-31].

Mechanism of Action

Catheter-based RDN operates by altering sympathetic renal activity through the disruption of both afferent and efferent nerve fibers located in the renal artery adventitia via a minimally invasive procedure [32, 33]. The RDN catheters employ thermal or chemical ablation methods to interrupt renal sympathetic nerve signaling. Ultrasound and radiofrequency-based catheters achieve this through thermal ablation, while alcohol denervation utilizes chemical ablation delivered via a three-needle device [34, 35].

Although pharmacological therapy has proven effective in reducing the risk of coronary heart disease, stroke, and heart failure, it remains unclear whether RDN can provide the same benefits. Further research is needed to establish this, despite observational studies and meta-analyses suggesting positive effects on target organ damage [36, 37].

Challenges to Implementation

Procedural and Technical Challenges

Operator Skill and Experience: Successful RDN requires highly skilled operators to perform the procedure accurately and safely. Variability in operator experience can impact outcomes, necessitating extensive training and certification programs.

Standardization of Techniques: There is a lack of standardization in RDN techniques and protocols, leading to variations in procedural success and patient outcomes. Establishing standardized guidelines is essential for consistent results.

Device and Technology Limitations: The development and refinement of RDN devices continue to evolve. Differences in device efficacy, safety profiles, and costs need to be addressed to optimize the use of RDN.

Clinical Challenges

Patient Selection: Identifying appropriate candidates for RDN is crucial. Factors such as comorbid conditions, anatomy of renal arteries, and baseline BP levels influence the selection process. Misidentification can lead to suboptimal outcomes.This is particularly one of the most difficult aspects to RDN implementation.

Long-term Efficacy and Safety: Long-term data on the efficacy and safety of RDN are still limited. Ongoing studies are required to confirm sustained BP reductions and assess potential long-term adverse effects.

Regulatory and Economic Challenges

Regulatory Approvals: RDN devices must undergo rigorous regulatory evaluations to ensure safety and efficacy. The approval process can be lengthy and varies by region, potentially delaying access to new technologies. As of November 2023, ultrasound and radiofrequency renal denervation have gained FDA approval

Cost and Reimbursement: The cost of RDN procedures and devices can be high. Ensuring adequate reimbursement from healthcare systems and insurance providers is essential to make the therapy accessible to patients. This means less likely access to the underserved population further bridging health disparities.

Healthcare Infrastructure: Implementing RDN requires well-equipped healthcare facilities with advanced imaging and procedural capabilities. Infrastructure limitations in certain regions may hinder widespread adoption.

Recent Advances in RDN

Ultrasound RDN

The introduction of a non-invasive ultrasound (US) RDN therapy presents a more appealing method for renal nerve ablation. This technique uses externally focused energy with a diagnostic Doppler device for precise targeting and tracking. Originally developed by Kona Medical Inc. in California, at least six trials have validated its BP-lowering efficacy in humans [38]. However, a recent sham-controlled trial did not show significant differences between the sham group and the US RDN group, although a greater ambulatory BP (ABP) change was noted in the US RDN group due to BP stabilization at baseline [39].

Alcohol-Mediated RDN

A recent trial involving 45 patients with uncontrolled hypertension on multiple medications showed that bilateral infusion of 0.6 ml of alcohol per artery resulted in significant BP reductions. Ambulatory BP decreased by 11/7 mmHg (95% CI, -15 to -7/-9 to -4 mmHg) and office BP by 18/10 mmHg (95% CI, -25 to -12/-13 to -6 mmHg) at six months [28]. The procedure was relatively short and exhibited a favorable safety profile. Two larger randomized, sham-controlled trials, TARGET BP OFF-MED and TARGET BP 1, are currently underway to further investigate these findings [40].

Catheter-based renal denervation continues to evolve as a promising therapy for resistant hypertension, driven by advancements in technology and clinical research. While challenges and uncertainties remain, ongoing trials and studies aim to refine the techniques and validate their long-term efficacy and safety. Addressing the procedural, clinical, regulatory, and economic challenges will be crucial for the widespread adoption and success of RDN. As research progresses, RDN has the potential to significantly impact the management of hypertension and improve patient outcomes.

2. Baroreflex Amplification

Baroreflex amplification is an innovative approach to managing resistant hypertension (RH) through peripheral neuromodulation. This method leverages the body's natural baroreflex mechanism, where increased blood pressure (BP) levels stimulate stretch-sensitive baroreceptors located in the carotid sinus and aortic arch. This stimulation triggers a rapid negative feedback loop that enhances afferent signaling and reduces efferent sympathetic outflow, leading to decreased heart rate and total peripheral resistance. Consequently, BP returns to an adequate level [40].

Historical Context and Technological Evolution

Baroreceptor stimulation was initially studied in the nineteenth century, marking the first generation of research in this field. However, early attempts were abandoned due to technological and safety concerns. Approximately two decades ago, with advancements in medical technology and the increasing focus on device-based therapies for RH, baroreflex amplification experienced a revival.

Clinical Trials and Developments

First-Generation Trials

The Rheos Pivotal Trial [41] represented the first generation of baroreflex amplification trials. Despite its pioneering nature, the trial did not achieve Food and Drug Administration (FDA) approval and was consequently discontinued.

Second-Generation Trials

A more recent cohort study involving the Barostim Neo device demonstrated long-term efficacy in systolic blood pressure (SBP) control, achieving levels below 140 mmHg in 25 out of 50 patients [42]. However, further randomized controlled clinical trials are necessary to validate its effects on ambulatory BP.

Endovascular Baroreflex Amplification (EVBA)

Studies are ongoing to develop less invasive devices that stimulate the baroreflex region, such as the Endovascular Baroreflex Amplification (EVBA) MobiusHD device. This device is designed to be implanted inside the carotid sinus. Experimental studies comparing a conventional self-expanding stent with the MobiusHD device have shown immediate and sustained BP-lowering effects, with MobiusHD also demonstrating a better safety profile [43].

The CALM-FIM study, the first-in-man trial conducted across Europe and USA centers in May 2013, reported significant reductions in office blood pressure (OBP), both systolic and diastolic, after six months (24 and 12 mmHg, respectively) [43]. After three years, SBP decreased by 30 mmHg, further supporting the efficacy of this approach. However, adverse safety endpoints were recorded in five patients, necessitating immediate interventions for hypotension, worsening hypertension, and infections [43].

Ongoing Trials

Current trials, such as CALM-2, a prospective, randomized, double-blind, sham-controlled pivotal study, are thoroughly evaluating EVBA with the MobiusHD device. The primary outcome of these studies is the change in mean 24-hour systolic ambulatory blood pressure (ABP) over six months.

Challenges to Implementation

Technological Challenges

Device Complexity: The complexity of baroreflex amplification devices requires sophisticated technology and precise engineering to ensure efficacy and safety. Continuous innovation and improvement are necessary to enhance device performance and patient outcomes.

Long-Term Efficacy and Durability: Ensuring the long-term efficacy and durability of baroreflex amplification devices remains a significant challenge. Devices must maintain their performance over extended periods without causing adverse effects.

Clinical Challenges

Patient Selection: Identifying suitable candidates for baroreflex amplification is crucial. Patients must be carefully selected based on their specific medical conditions, anatomy, and response to previous treatments to maximize the benefits and minimize risks.

Adverse Events Management: Managing adverse events such as hypotension, worsening hypertension, and infections is critical. The incidence of such events must be minimized through improved device design and procedural techniques.

Regulatory and Economic Challenges

Regulatory Approvals: Baroreflex amplification devices must undergo stringent regulatory evaluations to ensure their safety and efficacy. The regulatory process can be time-consuming and varies by region, potentially delaying patient access to new treatments.

Cost and Reimbursement: The high cost of baroreflex amplification devices and procedures poses a challenge. Ensuring adequate reimbursement from healthcare systems and insurance providers is essential to make this therapy accessible to a broader patient population.

Healthcare Infrastructure: Implementing baroreflex amplification requires advanced healthcare facilities with specialized equipment and trained personnel. Infrastructure limitations in certain regions may hinder the widespread adoption of this technology.

Baroreflex amplification represents a promising alternative to renal denervation for managing resistant hypertension [40]. With ongoing advancements in technology and clinical research, this method has the potential to provide significant benefits in BP control. However, addressing the technological, clinical, regulatory, and economic challenges is essential for the successful implementation and widespread adoption of baroreflex amplification. Continued research and innovation are critical to overcoming these challenges and improving patient outcomes in the management of resistant hypertension.

3. Arteriovenous Malformation

The ROX coupler device functions by creating a fixed-diameter (typically 4mm) arteriovenous (AV) anastomosis between the external iliac artery and vein. This connection links a low-resistance, high-compliance venous segment to the central arterial tree, resulting in an immediate reduction in blood pressure (BP). The coupling leads to a decrease in systemic vascular resistance and an increase in cardiac output, contributing to the overall reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) [44, 45, 46, 47].

Clinical Trials and Evidence

Initial Development and COPD Treatment

The ROX coupler was initially developed to treat chronic obstructive pulmonary disease (COPD) by increasing mixed venous oxygen saturation. In an open-label study involving 24 patients with COPD, the creation of an AV fistula (AVF) unexpectedly resulted in reduced systemic vascular resistance and increased cardiac output, which led to a notable drop in both SBP and DBP from baseline to the 12-month follow-up [45, 48]. This phenomenon is similar to the reduction in BP observed in patients with end-stage renal disease following AVF creation [48].

ROX CONTROL-HTN Study

The efficacy of the ROX coupler in treating resistant hypertension (RH) was further demonstrated in the ROX CONTROL-HTN study. This study involved 83 patients with RH and showed a significant mean systolic reduction of 13.5 ± 18.8 mmHg in patients with the AV coupler, compared to a negligible change of 0.5 ± 15.8 mmHg in the control group [48]. One-year follow-up data indicated a sustained reduction in both office blood pressure (OBP) and ambulatory blood pressure (ABP). Specifically, OBP showed a decrease of SBP by 25.1 ± 23.3 mmHg and DBP by 20.8 ± 13.3 mmHg ($P < 0.0001$ for both), while ABP demonstrated a reduction

in SBP by 12.6 ± 17.4 mmHg and DBP by 15.3 ± 9.7 mmHg (P < 0.0001) [44]. Additionally, there was a sustained reduction in isolated systolic hypertension [47].

Challenges to Implementation

Technological and Procedural Challenges

Device Placement and Technical Expertise: The creation of an AV anastomosis requires precise surgical skill and expertise to ensure accurate placement and minimize complications. Misplacement or technical errors can lead to ineffective outcomes or adverse events.

Long-Term Device Durability: Ensuring the long-term functionality and durability of the ROX coupler device is critical. Devices must withstand the physiological stresses over time without degrading or causing complications.

Clinical Challenges

Patient Selection and Suitability: Identifying suitable candidates for the ROX coupler procedure is essential. Patients must be carefully evaluated to ensure they are appropriate for the device, considering their overall health, comorbid conditions, and specific anatomical factors.

Management of Potential Complications: The potential risk of iliac venous stent complications, such as thrombosis or stenosis, poses a significant clinical challenge. Effective management and prompt intervention are necessary to address these complications and ensure patient safety.

Regulatory and Economic Challenges

Regulatory Approval and Compliance: The ROX coupler device must meet stringent regulatory standards to ensure its safety and efficacy. Obtaining and maintaining regulatory approval across different regions can be a complex and time-consuming process.

Cost and Reimbursement: The high cost of the ROX coupler device and associated procedural expenses can be a barrier to widespread adoption. Ensuring adequate reimbursement from healthcare systems and insurance providers is crucial to make this therapy accessible to a broader patient population.

Healthcare Infrastructure and Training: Implementing the ROX coupler procedure requires advanced healthcare facilities equipped with specialized tools and personnel trained in the technique. Developing and maintaining such infrastructure can be challenging, especially in resource-limited settings.

The ROX coupler device offers a promising solution for managing resistant hypertension through its unique mechanism of creating an AV anastomosis. Clinical trials have demonstrated its efficacy in significantly reducing blood pressure [44-47]. However, the successful implementation of this technology faces several challenges, including technological, clinical, regulatory, and economic hurdles. Addressing these challenges through ongoing research, improved device design, and robust clinical protocols is essential to fully realize the potential of the ROX coupler device in hypertension management.

4. Carotid Body (CB) Ablation

Mechanism of Action

The carotid body, situated at the carotid bifurcation, is a crucial peripheral chemoreceptor in humans. It plays a significant role in regulating respiratory and cardiovascular responses to changes in blood oxygen, carbon dioxide, and pH levels. The carotid sinus nerve, which innervates the carotid body, is involved in these regulatory processes. Animal experimental trials have demonstrated that carotid sinus nerve denervation can lead to reduced blood pressure (BP) levels [49] .

Building on this concept, the Cibiem transvenous ultrasound system employs a minimally invasive approach to modulate carotid body activity [50]. This system uses ultrasound energy to target the carotid body, aiming to disrupt its function and consequently lower BP .

Clinical Trials and Evidence

Unilateral Surgical Carotid Body Resection

An early uncontrolled study assessed the effects of unilateral surgical carotid body (CB) resection in 15 patients with resistant hypertension (RH). The primary outcome was the change in average office and ambulatory systolic BP (SBP) over a 12-month follow-up period [50]. While the overall results did not show a

significant reduction in SBP, a subset of patients (8 out of 15) experienced notable reductions in daytime ambulatory SBP at 3 months (-23 ± 3 mmHg; P=0.0005) and 6 months (-26 ± 4 mmHg; P=0.0021), though this effect was not sustained at the 12-month follow-up [50] .

Transvenous Carotid Body Ablation

More recent advancements have focused on less invasive techniques. A multicenter, first-in-man study evaluated the efficacy of transvenous carotid body ablation in patients with RH. This method uses catheter-based ultrasound to ablate the carotid body. The study reported a significant reduction in 24-hour ambulatory BP (ABP), with an average decrease of 9.1/6.7 ± 13.5/8.7 mmHg [51] . These findings suggest that this less invasive approach might offer a promising alternative for BP management in RH patients.

Challenges to Implementation

Variability in Response

The variability in patient response to carotid body modulation poses a significant challenge. While some patients experience substantial BP reductions, others do not show significant improvements. Understanding the factors contributing to this variability is crucial for patient selection and optimizing treatment outcomes.

Long-term Efficacy and Safety

The long-term efficacy and safety of carotid body modulation need further investigation. The initial promising results must be validated through extended follow-up studies to ensure sustained BP control and identify any potential long-term adverse effects.

Technical and Procedural Challenges

The technical complexity of the procedure, especially for transvenous carotid body ablation, requires specialized skills and training. Ensuring that healthcare providers are proficient in these techniques is essential for minimizing procedural risks and improving patient outcomes.

Patient Selection

Identifying the appropriate candidates for carotid body modulation is critical. Not all patients with RH may benefit from this intervention, and precise criteria need to be developed to ensure that only those most likely to respond are selected for the procedure.

Cost and Resource Allocation

The cost of developing, implementing, and maintaining the necessary technology for carotid body modulation can be substantial. Ensuring that these procedures are cost-effective and accessible to a broad patient population is essential for widespread adoption.

Regulatory and Ethical Considerations

Regulatory approval processes and ethical considerations surrounding novel medical interventions must be thoroughly addressed. Ensuring that all trials are conducted with rigorous oversight and that patient safety is prioritized will be key to gaining regulatory approval and public trust.

Carotid body modulation represents a novel approach to managing resistant hypertension, leveraging the body's own regulatory mechanisms to achieve BP control. Despite the promising early results from clinical trials, several challenges must be addressed to ensure its successful implementation. These include variability in patient response, the need for long-term efficacy data, technical complexities, patient selection criteria, cost considerations, and regulatory hurdles. Addressing these challenges through continued research, training, and careful clinical implementation will be crucial for realizing the full potential of this innovative treatment.

5. Pacemaker-Based Cardiac Neuromodulation

Pacemaker-based cardiac neuromodulation has emerged as a promising approach for managing hypertension, particularly in patients who already require pacemaker implantation [52]. This innovative technique leverages the capabilities of pacemaker technology to modulate cardiac function and subsequently reduce blood pressure (BP).

Mechanism of Action

The primary objective of pacemaker-based cardiac neuromodulation is to reduce BP by modulating left ventricular ejection volume [52]. This is achieved through repeated adjustments of the atrioventricular (AV) intervals. The Moderato system, a key player in this approach, mimics a dual-chamber structure to optimize heart rhythm and reduce BP. By altering the timing of ventricular contractions, the system can influence cardiac output and vascular resistance, leading to a reduction in BP.

Clinical Trials and Evidence

MODERATO-1 Study

The MODERATO-1 study was a pivotal trial that assessed the efficacy of the BackBeat Moderato system. This study enrolled thirty-five patients with systolic BP exceeding 140mmHg despite the use of antihypertensive medications. Upon activation of the device, patients experienced a significant and immediate drop in BP, with a reduction of 24mmHg in office systolic BP at the 3-month follow-up mark [53] . This substantial decrease highlighted the potential of the Moderato system to effectively manage hypertension in pacemaker patients.

MODERATO-II Studies

The subsequent MODERATO-II studies further supported the findings of the initial trial. These studies revealed a noteworthy drop of 11mmHg in systolic BP among patients using the BackBeat Moderato system, without significant adverse outcomes [54]. This evidence underscores the system's efficacy and safety in managing hypertension in patients requiring pacemakers.

Advantages and Applicability

One of the most significant advantages of pacemaker-based cardiac neuromodulation is its applicability to patients who already need a pacemaker. For these patients, the Moderato system offers a tailored approach to BP control, integrating seamlessly with existing cardiac management strategies. This dual benefit of addressing both pacing needs and hypertension makes it an attractive option for a specific patient population.

Challenges to Implementation

Limited Applicability

The primary challenge of this approach is its limited applicability. Pacemaker-based cardiac neuromodulation is inherently restricted to patients who require pacemaker insertion. This limits the potential patient population and may not be suitable for those with hypertension but without an indication for a pacemaker [55].

Adverse Effects and Safety Concerns

While the MODERATO studies reported minimal significant adverse outcomes, the potential for adverse effects remains a concern. Adjusting the AV intervals to modulate BP could theoretically exacerbate conditions like heart failure in susceptible patients. Continuous monitoring and robust safety protocols are essential to mitigate these risks.

Cost and Resource Allocation

The implementation of pacemaker-based cardiac neuromodulation involves considerable costs, both for the technology itself and for the surgical procedures required for pacemaker implantation. This could pose a financial burden on healthcare systems and patients, potentially limiting widespread adoption.

Need for Specialized Training

Healthcare providers need specialized training to effectively implement and manage pacemaker-based cardiac neuromodulation. This includes understanding the intricacies of the Moderato system and being adept at adjusting AV intervals to optimize BP control without compromising cardiac function.

Long-Term Efficacy and Research

Long-term efficacy and safety data are still required to fully establish the benefits and risks of pacemaker-based cardiac neuromodulation. Ongoing research and extended follow-up studies are necessary to validate the initial positive outcomes and ensure sustained BP control over time.

Pacemaker-based cardiac neuromodulation represents an innovative approach to hypertension management, particularly suited for patients who already require pacemaker implantation. The BackBeat Moderato system has shown significant potential in reducing BP, as evidenced by the MODERATO-1 and MODERATO-II studies. However, the implementation of this technology faces challenges, including limited applicability, potential adverse effects, high costs, the need for specialized training, and the necessity for long-term efficacy data. Addressing these challenges through continued research, training, and cost-management strategies will be crucial for maximizing the benefits of this promising approach to hypertension control.

6. Electro-acupuncture

Electro-acupuncture, initially developed for the treatment of peripheral pain syndrome, has unexpectedly demonstrated efficacy in blood pressure (BP) reduction. This technique involves the stimulation of the median nerve, which is thought to modulate the sympathetic nervous system, thereby influencing cardiovascular function and leading to lowered BP levels.

Clinical Trials and Evidence

Electro-acupuncture has been the subject of various clinical trials aimed at assessing its effectiveness in BP management. One notable study involved the use of the eCoin device, a minimally invasive electro-acupuncture device that delivers low-frequency electrical stimulation. This device is designed to provide 30 minutes of stimulation weekly, targeting the median nerve bilaterally.

Key Findings

In a recent sham-controlled trial utilizing the eCoin device, significant reductions in BP were observed. The study reported a mean BP reduction of over 10 mmHg after six months of treatment. This result highlights the potential of electro-acupuncture as a viable non-pharmacological intervention for hypertension management [56].

Regulatory and Approval Status

Despite facing funding challenges during its development and trial phases, the eCoin device demonstrated sufficient efficacy and safety to gain regulatory approval. In March 2022, the device received approval from the U.S. Food and Drug Administration (FDA) for the treatment of urinary urge incontinence, further validating its therapeutic potential [57].

Broader Implications and Potential

The successful application of electro-acupuncture for BP reduction has broader implications for its use in various medical conditions. Its mechanism of action through sympathetic nervous system modulation opens avenues for exploring its benefits in other autonomic dysfunction-related disorders. Furthermore, its minimally invasive nature makes it an attractive option for patients seeking alternatives to traditional pharmacological treatments.

Challenges to Implementation

Funding and Resource Allocation: The development and widespread adoption of electro-acupuncture devices like eCoin require substantial financial investment. Initial trials faced significant funding challenges, which could impede further research and development efforts.

Standardization and Protocol Development: There is a need for standardized treatment protocols to ensure consistent and reproducible results across different clinical settings. Variability in stimulation parameters and techniques can affect the outcomes and efficacy of the treatment.

Healthcare Provider Training: Effective implementation of electro-acupuncture in clinical practice necessitates comprehensive training programs for healthcare providers. Ensuring that practitioners are skilled in the correct application of the technique is crucial for its success.

Patient Acceptance and Compliance: Patient acceptance of electro-acupuncture as a treatment modality can vary. Factors such as the invasiveness of the procedure, cultural perceptions of acupuncture, and the need for regular treatment sessions may influence patient compliance.

Long-Term Efficacy and Safety: While short-term results are promising, the long-term efficacy and safety of electro-acupuncture for BP management require further investigation. Longitudinal studies are needed to assess the sustainability of BP reductions and monitor for potential adverse effects over extended periods.

Integration into Healthcare Systems: Incorporating electro-acupuncture into existing healthcare systems poses logistical challenges. Ensuring seamless integration with current hypertension management protocols and facilitating reimbursement through insurance systems are essential steps for widespread adoption.

Electro-acupuncture represents a promising alternative for BP management, leveraging the modulation of the sympathetic nervous system through median nerve stimulation [56]. The clinical evidence, particularly from studies using the eCoin device, underscores its potential benefits. However, addressing the challenges related to funding, standardization, training, patient acceptance, long-term efficacy, and healthcare integration is crucial for realizing its full potential and ensuring its successful implementation in clinical practice.

7. Deep Brain Stimulation

First introduced by Green Alexander Laurence in 2007, deep brain stimulation (DBS) emerged as a promising technique for reducing blood pressure (BP) through targeted central nervous system stimulation. Initial studies revealed a substantial BP reduction of 25/8.4 mmHg when employing stimulation parameters set at 2V and 30Hz [58]. Subsequent cases further validated its efficacy; notably, a patient with chronic pain syndrome experienced a BP reduction of 33/13 mmHg following 27 months of sustained stimulation [59].

DBS involves the implantation of electrodes within specific brain regions, where electrical impulses are used to modulate neural activity. This technique has been widely adopted for managing neurological disorders such as Parkinson's disease, essential tremors, and dystonia [58]. Its mechanism of action in BP reduction is hypothesized to involve the modulation of autonomic pathways that regulate cardiovascular function.

Despite its therapeutic potential, several challenges impede the widespread adoption of DBS for hypertension management:

High Costs: The procedure is expensive, involving the costs of surgery, the implantation of the device, and ongoing maintenance and adjustments of the system. These financial barriers make it less accessible for many patients and healthcare systems [60].

Surgical Risks: As with any invasive surgical procedure, DBS carries risks such as infection, hemorrhage, and adverse reactions to anesthesia. These risks necessitate a careful patient selection process and comprehensive preoperative evaluation.

Technical Complexity: The success of DBS requires precise placement of electrodes, which demands advanced imaging techniques and specialized surgical expertise. The complexity of the procedure can limit its availability to centers with highly skilled neurosurgical teams.

Postoperative Management: DBS requires ongoing management, including regular follow-ups for device adjustments and monitoring for potential complications. This need for continual care can be burdensome for both patients and healthcare providers.

Variable Efficacy: While initial results are promising, the long-term efficacy of DBS for BP management remains under investigation. Variability in patient responses necessitates further research to identify the predictors of success and to optimize stimulation parameters.

Ethical and Psychological Considerations: The implantation of a brain device raises ethical questions and concerns about the psychological impact on patients. Issues such as consent, autonomy, and the potential for changes in personality or cognitive function must be carefully considered.

While deep brain stimulation offers a novel and potentially effective approach to hypertension management, significant challenges related to cost, surgical risks, technical complexity, and long-term efficacy need to be addressed. Ongoing research and advancements in technology are essential to overcoming these barriers and expanding the use of DBS in clinical practice.

Table *1* below summarizes the available device therapies:

Device-Based Therapies	Description
Renal Denervation (RDN)	Renal Denervation (RDN) remains a prominent therapy for Resistant Hypertension (RH), comprising almost 70% of RH therapy coverage.
	RDN systems are clinically approved and rely on device-based technology but do not permanently reside in the body.
Baroreflex Amplification	Baroreflex Amplification utilizes peripheral neuromodulation to control blood pressure (BP) by stimulating baroreceptors, reducing sympathetic outflow, heart rate, and peripheral resistance.
Arteriovenous Malformation	Arteriovenous Malformation involves creating an arteriovenous anastomosis to reduce BP. The ROX coupler device and other approaches have shown efficacy in reducing systemic vascular resistance and BP.
Carotid Body (CB) Ablation	CB Ablation aims to modulate carotid body activity to reduce BP. Methods include surgical resection and catheter-based ultrasound modulation. Studies show varying results in BP reduction.
Pacemaker-Based Cardiac Neuromodulation	This approach modulates left ventricular ejection volume through pacemakers to control BP. Studies demonstrate immediate BP reduction upon device activation without significant adverse effects.
Electro-acupuncture	Electro-acupuncture, primarily used for pain relief, has shown potential in reducing BP through median nerve stimulation. Studies demonstrate significant BP reduction after regular low-frequency stimulation.
Deep Brain Stimulation	Deep Brain Stimulation, initially developed for neurological conditions, has shown promise in reducing BP through central nervous system stimulation. Studies report substantial BP reduction with long-term stimulation.

TABLE 1: Device therapies summary table

Future Directions

In the landscape of hypertension management, the future unfolds with promising avenues based on the insights gained from this comprehensive review of device-based therapies. As we navigate the evolving realm of cardiovascular health, several key directions emerge:

1. Precision Refinement of Renal Denervation: Further research is imperative to refine and personalize Catheter-Based Renal Denervation. Investigating advanced technologies, procedural techniques, and patient selection criteria will optimize the efficacy of this widely utilized therapy for resistant hypertension. Emphasis should be placed on longitudinal studies to assess its impact on cardiovascular outcomes and ascertain whether it confers benefits akin to pharmacological therapy.

2. Innovations in Baroreflex Amplification: The exploration of Baroreflex Amplification holds promise as a less invasive alternative. Ongoing trials with devices like the Endovascular Baroreflex Amplification (EVBA) Mobius HD present opportunities for innovation. Future endeavors should delve into the development of less invasive devices, assess long-term ambulatory blood pressure effects, and conduct rigorous randomized controlled clinical trials to confirm efficacy.

3. Advancements in Arteriovenous Malformation Interventions: The ROX coupler device shows potential in addressing resistant hypertension through arteriovenous malformation. Future research should focus on refining the device design, evaluating its safety profile, and exploring its application in broader patient populations. Additionally, efforts should be directed toward minimizing potential risks associated with iliac venous stents.

4. Unraveling the Potential of Carotid Body Ablation: Carotid Body (CB) Ablation, particularly with the Cibiem transvenous ultrasound system, requires further investigation. Studies should aim to understand its sustained efficacy, safety profile, and potential impact on office and ambulatory blood pressure. Larger randomized controlled trials are needed to ascertain its role in managing resistant hypertension.

5. Integration of Pacemaker-Based Cardiac Neuromodulation: The potential of Pacemaker-Based Cardiac Neuromodulation for hypertensive control, especially in pacemaker patients, warrants continued exploration. Future studies should delve into its applicability, long-term effects, and adverse outcomes, considering its viability as an option for those with resistant hypertension requiring pacemaker insertion.

6. Validating Electro-acupuncture Efficacy: Electro-acupuncture, with its promising BP reduction effects, requires further validation through well-designed trials. Continued research should assess its long-term impact, scalability, and integration into routine clinical practice. Overcoming funding challenges is crucial

to unlock its potential as a minimally invasive strategy for hypertension management.

7. Cost-Effective Implementation of Deep Brain Stimulation: While Deep Brain Stimulation has shown significant BP reduction in various conditions, its adoption for hypertension management faces cost-related challenges. Future efforts should focus on optimizing the cost-effectiveness of this intervention, exploring its utility in specific patient subsets, and addressing barriers to broader implementation.

As we embark on these future directions, collaborative efforts among researchers, clinicians, and policymakers are essential to translate these insights into tangible advancements, ultimately enhancing the landscape of device-based therapies for resistant hypertension.

Conclusions

In conclusion, the escalating global burden of hypertension necessitates continual advancements in treatment strategies. Device-based therapies, such as Catheter-Based Renal Denervation, Baroreflex Amplification, Arteriovenous Malformation, Carotid Body Ablation, Pacemaker-Based Cardiac Neuromodulation, Electro-acupuncture, and Deep Brain Stimulation, offer promising avenues for managing resistant hypertension.

The evolving landscape, marked by FDA-approved Ultrasound and Radiofrequency Renal Denervation, underscores the significance of innovative interventions. While challenges persist, ongoing research emphasizes safety, efficacy, and long-term outcomes. As we navigate this complex terrain, these therapies showcase the potential to revolutionize hypertension management, providing hope for improved patient outcomes and addressing the critical need for effective solutions in the face of resistant hypertension.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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