International Journal of Cardiology 214 (2016) 320–330

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Neural modulation for hypertension and heart failure

S. Smith [a,*], P. Rossignol [b], S. Willis [a], F. Zannad [b], R. Mentz [c], S. Pocock [d], J. Bisognano [e], Y. Nadim [f], N. Geller [g], S. Ruble [h], C. Linde [i,**]

[a] The Ohio State University Wexner Medical Center, Department of Internal Medicine and Division of Cardiology, Columbus, OH, USA
[b] Inserm, CIC 1433, Centre Hospitalier Universitaire, Universite´ de Lorraine, F-CRIN INI-CRCT, Nancy, France
[c] Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, NC, USA
[d] Medical Statistics Unit LSHTM, London, UK
[e] University of Rochester Medical Center, Department of Medicine, Cardiology, Rochester, NY, USA
[f] CVRx, Inc, Minneapolis, MN, USA
[g] Office of Biostatistics Research, Division of Cardiovascular Sciences, NHLBI, National Institutes of Health, Bethesda, MD, USA
[h] Boston Scientific CRV, St. Paul, MN, USA
[i] Institution of Internal Medicine, Karolinska Institutet and Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 29 January 2016
Accepted 19 March 2016
Available online 4 April 2016

Keywords:
Hypertension
Heart failure
Neural modulation
Renal denervation
Baroreceptor

ABSTRACT

Hypertension (HTN) and heart failure (HF) have a significant global impact on health, and lead to increased morbidity and mortality. Despite recent advances in pharmacologic and device therapy for these conditions, there is a need for additional treatment modalities. Patients with sub-optimally treated HTN have increased risk for stroke, renal failure and heart failure. The outcome of HF patients remains poor despite modern pharmacological therapy and with established device therapies such as CRT and ICDs. Therefore, the potential role of neuromodulation via renal denervation, baro-reflex modulation and vagal stimulation for the treatment of resistant HTN and HF is being explored. In this manuscript, we review current evidence for neuromodulation in relation to established drug and device therapies and how these therapies may be synergistic in achieving therapy goals in patients with treatment resistant HTN and heart failure. We describe lessons learned from recent neuromodulation trials and outline strategies to improve the potential for success in future trials. This review is based on discussions between scientists, clinical trialists, and regulatory representatives at the 11th annual CardioVascular Clinical Trialist Forum in Washington, DC on December 5–7, 2014.

1. Introduction

Hypertension (HTN) is a major risk factor for cardiovascular disease and heart failure (HF). Despite therapeutic advances cardiovascular morbidity [1,2] and mortality remains high both in real life mortality [3] and as evidenced by randomized controlled trials [4]. The autonomic nervous system (ANS) plays a crucial role in the development of organ damage due to HTN and potentially in the transition of HTN to heart failure with preserved or reduced ejection fraction. In HF the ANS initially plays a critical compensatory role in maintaining cardiovascular homeostasis in the failing heart. Over time the deleterious effects dominate since a decrease in cardiac output leads to activation of the renin angiotensin–aldosterone system (RAAS) and increase in sympathetic nerve activity, resulting in increased morbidity and mortality [5]. Device based modulation of the ANS therefore is theoretically attractive as an additional therapy both in HTN and HF.

Currently, the clinical usefulness of new devices that modulate the autonomic nervous system including renal denervation, carotid baroreceptor stimulation and vagal nerve stimulation are being explored in randomized controlled trials in HTN and HF. At the same time new advances in heart failure medication that modify the RAAS system are being made both for HF [6] and for HTN by use of existing drugs [7]. The experience gained through randomized controlled studies (RCT) of cardiac resynchronization therapy (CRT) confirmed that the combination of heart failure medication with devices can have a synergistic therapeutic effect [8]. Combining different therapeutic approaches will likely surpass the clinical effect of a single approach in reducing morbidity and mortality, and halt or revere the disease state.

The aim of this review is to discuss the background and rationale for devices that modify the ANS for therapy resistant HTN and HF. Preclinical and clinical data, challenges involved and the trialists' view, with particular focus on how drugs and devices may interact and their role for the future are given. The review is based on discussions between scientists, clinical trialists and regulatory representatives at the 11th

* Correspondence to: S. Smith, Division of Cardiology, The Ohio State University, 473 West 12th ave Suite 200, Columbus, OH 43210, USA.
** Correspondence to: C. Linde, Department of Cardiology, N205, Karolinska University Hospital, Solna, 117 76 Stockholm.
E-mail addresses: sakima.smith@osumc.edu (S. Smith), cecilia.linde@ki.se (C. Linde).

http://dx.doi.org/10.1016/j.ijcard.2016.03.078
0167-5273/

Global Cardio Vascular Clinical Trialists' Forum in Washington, DC, December 5–7, 2014.

1.1. Clinical background for therapy resistant hypertension and heart failure

1.1.1. Hypertension

The Eighth Joint National Committee [9] and the European Guidelines for hypertension [10] have set their blood pressure (BP) therapy goal at 140/90 mm Hg for most patients, and 150/90 for those over 60 years of age. Most guidelines also recommend ambulatory BP (ABPM) to confirm treatment resistant hypertension (TRH) and distinguish it from white coat hypertension. Around 10–20% of HTN patients have TRH which is defined as a seated office systolic blood pressure >140 or diastolic BP ≥ 90 mm Hg on maximally tolerated doses of at least three anti-hypertensive medications, one of which must be a diuretic [11]. TRH is more common in the elderly, in patients with impaired renal function, diabetes and the obese [12].

The mechanisms for TRH appear to be multifactorial [13]. ANS activation and sodium retention are among the more important pathophysiological factors. Renal sympathetic efferent and afferent nerves located within and immediately adjacent to the wall of the renal artery, are crucial for the initiation and maintenance of systemic HTN [14,15]. While patients with TRH are known to have increased plasma volume and elevated systemic vascular resistance with a normal cardiac output, the mechanisms underlying this abnormal hemodynamic pattern are unknown [16,17].

TRH patients therefore constitute a therapeutic challenge since there is no firm strategy of how to reach normal BP, and the choice of additional (4th) medication is based on the physicians´ judgment. Moreover, some patients may not reach target pressures despite additional medications, do not tolerate additional drugs or are non-compliant to the prescribed drug therapy regiment.

The autonomic nervous system (ANS) has a significant role in the pathophysiology of HF and TRH [18,19]. Initially, this serves as compensatory mechanisms to maintain adequate tissue perfusion through an increase in sympathetic and a decrease in parasympathetic tone over time the alterations in the ANS begin to worsen cardiac pathophysiology and increases peripheral vascular resistance, which in turn leads to worsening of HF and hypertension. Modifications of the ANS on a structural level new treatments such renal denervation or carotid stimulation/baroreceptor activation may alter autonomic tone and improve refractory HTN and HF [19].

1.1.2. Heart failure

Mortality has improved in HF patients over the last decade(s) due to the introduction of drug therapy by targeting the renin–angiotensin–aldosterone system [20–22](RAAS). Further reductions in morbidity and mortality have been achieved by the addition of CRT (10–30%) in patients with conduction abnormalities [23–28]. In routine medical practice the mortality in HF is higher than in RCTs, highlighting the need for additional therapies [3].

Most recently LCZ 696, which is a combination of valsartan and neprilysin, has proved to be a valuable addition to the heart failure pharmacological regiment. In the PARADIGM HF trial, LCZ 696 was shown to have marked effects on heart failure hospitalizations and total mortality (17% over 27 months) when compared to the conventional first therapy choice of enalapril (19.8%) [6]. Ivabradine, another relatively new drug, also has positive morbidity and mortality (5% and 2% compared to placebo, respectively) effects by modification of heart rate by blocking the I_F channels. It is indicated in those patients who remain in high rate sinus rhythm (>70 bpm) despite beta-blockers treatment or have an intolerance to beta-blockers [29,30].

Patients eligible for CRT often do not tolerate the recommended doses of guideline indicated HF medications. In particular, beta-blockers are often prescribed in suboptimal doses due to hypotension and/or bradycardia. The hemodynamic improvement with the addition of CRT, and the subsequent prevention of bradycardia by pacing, enables the up-titration of beta-blockers and other HF medication. This leads to a synergistic effect that enhances reverse left ventricular remodeling [8]. The improvements are sometimes so profound that diuretic doses with the potential of damaging renal function can often be lowered or discontinued. In patients that still show little improvement with guideline indicated treatment, therapies which alter the ANS may provide a much needed addition to the HF and TRH arsenal.

1.2. Renal denervation for treatment resistant hypertension—background, rationale and preclinical data

In experimental studies, the renal nerves have been demonstrated to stimulate the secretion of renin from the juxtaglomerular apparatus, which promotes renal tubular absorption of sodium and causes renal vasoconstriction, reducing renal blood flow and elevating BP responses [15,31]. Key to HTN pathogenesis is impairment of the normal capacity of the kidneys to excrete sodium at a higher arterial perfusion pressure — the pressure-natriuresis [32]. Impairment of this process is believed to be a central component of HTN. Renal denervation helps reverse this process by shifting the renal pressure natriuresis curve to the left, promoting urinary excretion of sodium and lowering of BP [18].

The development of the catheter based renal denervation was based on the BP lowering effect of surgical denervation, and an understanding of the anatomy of the postganglionic renal sympathetic nerves of the kidney [33]. Three criteria must be met for a successful RDN therapy: 1) Developing an intervention which could alter the activation of renal sympathetic nerves, 2) Building on the previous concept of the BP lowering effect of previous known surgical experimental models, and 3) An anatomical location of the postganglionic renal sympathetic nerves in the lumen of the kidney that would be accessible for catheter ablation [18].

Renal denervation for TRH aims at denervation of the renal afferent and efferent nerves to reduce renal sympathetic activity without the complications of the early surgical sympathectomy studies [34–36]. Renal denervation (RDN) can now be achieved by a catheter placed in the lumen of each renal artery. RDN is accomplished via circumferential, low energy radiofrequency applications using an external generator to ablate the nerves [13].

1.3. Clinical trials of RDN in hypertension

Studies of renal denervation have been focused on patients with TRH. Promising results from early observational and un-blinded studies [37,38] have not been consistently corroborated in randomized controlled studies, although the adverse events rates as whole have been relatively low (Table 1) [39].

The results of SYMPLICITY-1 [37], a small multicenter open label observational study demonstrated that catheter based RDN resulted in decreased and sustained office BP reduction over 3 years (Table 1). Patients with elevated 24-hour ambulatory BP were r enrolled and followed for change in 6-month office BP measurements [37]. There was a significant reduction in blood pressure following RDN [37]. The follow-up study, SYMPLICITY-2 [38], was designed as a randomized controlled trial using similar inclusion criteria to SYMPLICITY-1, but with the inclusion of a control group. The significant reduction in seated office BP seen in SYMPLICITY-2 was believed to be a result of successful renal denervation despite lack of a formal assessment of renal sympathetic activity [13]. Patients, investigators, and assessors of outcome, all were un-blinded, which may have significantly impacted (exaggerated) the primary endpoint in both studies [13]. SYMPLICITY-3 [39] was the first randomized double blind, sham control design with blinded endpoint evaluation. The results of the trials failed to demonstrate any favorable effect from RDN when compared to the sham group.