CROSSTALK

Comments on the CrossTalk opposing views: Which technique for controlling resistant hypertension? Carotid sinus stimulation, renal nerve ablation or carotid chemoreceptor denervation/modulation

Which technique for controlling resistant hypertension? Are we missing something?

Rob Shave and Eric Stohr
Cardiff Metropolitan University, UK

We read with great interest the recent CrossTalk debate in The Journal of Physiology (Jordan, 2014; Ratcliffe et al. 2014; Schlaich et al. 2014). All authors present convincing arguments to support different approaches to the management of resistant hypertension. However, given that exercise training reduces blood pressure in individuals with resistant hypertension (Dimeo et al. 2012), and can result in weight loss which has been shown to lower blood pressure further (Aucott et al. 2005), we found it surprising that at no point in the debate was reference made to exercise. Moreover, as exercise training meets many of the criteria suggested by Ratcliffe et al. 2014, is non-invasive, cost-effective and associated with a low risk of adverse events, surely it warrants consideration in relation to the management of resistant hypertension. It will not be lost to the readers of this debate that exercise training chronically increases parasympathetic tone and acutely stimulates the carotid sinus, both potential targets of the suggested approaches outlined in the debate. We note that the magnitude of blood pressure reduction possible with exercise may be limited (Calhoun et al. 2008) and that questions remain regarding the optimal dose and effective clinical prescription. Despite this, exercise training should not be overlooked as a potential adjunctive therapy in patients with resistant hypertension, especially as it is associated with wider health benefits than solely improving hypertension.

References


Additional information

Competing interests
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Resistant hypertension; three procedures same target

John H. Coote
School of Clinical and Experimental Medicine, University of Birmingham, UK

The three reports (Jordan, 2014; Schlaich et al. 2012; Ratcliffe et al. 2014) describing interventions to treat drug resistant hypertension in patients with a variety of organic impairments show that different approaches can have a degree of success in reducing systolic and diastolic blood pressure. One study suggests that carotid body chemoreceptors are critically involved, another that the cause lies in the renal innervation, whilst a third implies that an inadequate baroreceptor control allows higher vasomotor nerve activity. Each is based on sound experimental evidence. However, the common factor revealed by these treatments is a high sympathetic activity to heart and blood vessels. A cause could be down-regulation of inhibitory mechanisms in the cardiovascular centres in the brain so enhancing excitability of pre-sympathetic neurones that drive the output to cardiovascular organs. Therefore, it may not be that carotid body or the kidney is a source of an increased afferent traffic to the brain, but that the same level of signalling more easily facilitates central neurones. Since each treatment is somewhat daunting I wonder if it might be better to consider how to pharmacologically treat centrally driven SNA. For example the three afferent sources project to the hypothalamic pre-sympathetic paraventricular neurones (PVN) and a lesion here is dramatically potent in reducing hypertension in experimental animals (Allen, 2002). The PVN projection excites neurones via the release of vasopressin acting on V1a receptors (Yang et al. 2002) suggesting a clinical trial of the V1a non-peptide antagonist as a novel alternative.

References


Additional information

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None declared.

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Device development highlights importance of sympathetic mechanisms and individual differences

Nisha Charkoudian

US Army Research Institute of Environmental Medicine, Natick, MA, USA

The clinical problem of resistant hypertension, and the three exciting new approaches to treatment outlined in this CrossTalk, are excellent examples of the important insights afforded by integrative physiological approaches to medical device development. Two key points stand out in all three discussions. First, pathological sympathoexcitation is often a central factor in development of hypertension. This is in contrast to the ‘renal-centric’ view of hypertension which is still more commonly taught in medical school settings (Guyton et al. 1972), and reflects the growing recognition of the importance of sympathetic neural activity in long term blood pressure regulation (Schlaich et al. 2004; Hart et al. 2012). Second, all authors pointed out the importance of our (present or future) ability to assess individual responsiveness to a given therapy. For example, a hypertensive patient who is identified as having a high level of tonic input from carotid body chemoreceptors (‘high CB tone’; Ratcliffe et al. 2014) would be most likely to benefit from denervation or modulation of carotid chemoreceptors. A person with ‘low CB tone’ would not. The idea of ‘clinical phenotyping’ reinforces the importance of inter-individual variability in cardiovascular regulation, both in terms of maintenance of normotension (Hart et al. 2012; Charkoudian & Wallin, 2014) and development of hypertension (Schlaich, 2004; Hart et al. 2013). As this type of research moves forward, it will be of interest to see more prospective data from human subjects, and to evaluate whether easily identifiable factors (age, sex, obesity, etc.) tend to move patients into one category or another in terms of their likelihood to respond to one or another of these treatments. The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Army or the Department of Defense.

References


References


Additional information

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Baroreflexes do not set the level of blood pressure chronically

Irving H. Zucker

University of Nebraska Medical Center, Omaha, NE, USA

I read with interest Dr Jordan’s discussion of the important role of baroreflexes in blood pressure control and the potential role of carotid sinus stimulation in mediating a decrease in blood pressure and sympathetic nerve activity in patients with resistant hypertension. I certainly agree with the view that neuromodulation may have an important therapeutic benefit in these patients and potentially in other sympatho-excitatory states. We must, however, remember the difference between using this technique as a therapy in disease and the role of the baroreflexes in the long-term physiological control of blood pressure. It is well documented that baroreflex denervation does not increase mean blood pressure but rather increases blood pressure variability when measured in conscious animals (Cowley et al. 1973; Cornish & Gilmore, 1985). The control of blood pressure is multifactorial but chronically is related more to factors residing in the peripheral vessels and myocardium rather than buffer reflexes. The interventions described may override normal physiology in disease states.

References


Additional information

Competing interests

None declared.

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Comment on renal denervation versus carotid sinus stimulation

Paul M. Pilowsky
Heart Research Institute, Sydney, NSW, Australia

The use of device-based treatment in the form of activation of the carotid sinus, or denervation of renal nerves has garnered considerable enthusiasm recently. Unfortunately, there is very little clear evidence that either of these techniques is effective in the long-term. A key problem with hypertension is medication compliance. One physician famously commented at an International Society for Hypertension meeting that the British were considered to be the control group of Europe because they so rarely took their medication. Given that this is the case, and given the possibility of psychological overlay, leading to patients failing to take medication in order to receive continuing medical attention, it is my strong suggestion that in every case, treatment efficacy needs to be established rigorously prior to the use of expensive and invasive approaches. As a minimum, patients ought to be admitted to a facility and their medication intake monitored. Serum levels of medications should also be monitored to ensure that therapeutic levels are achieved. Given the known difficulties of achieving adequate renal nerve denervation, I suggest that all patients where this procedure is being recommended should first receive bilateral regional anaesthesia (e.g. bupivicaine) aimed at the hilus of the kidney. This ‘phenotyping’ approach would determine whether or not denervation of the kidney is likely to achieve a reduction in sympathetic nerve activity and arterial blood pressure.

Additional information

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None declared.
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One side or two?

David J. Collier, C. Calderwood, J. E. Angell-James, C. B. Wolff and A. H. Nickol
William Harvey Heart Centre, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Whilst unilateral carotid baroreceptor stimulation may be anticipated to be effective, as the last baroreceptor fibre removed in denervation experiments is the most influential, the assertion that unilateral carotid body resection reduces blood pressure seems more surprising, as elegant animal data from the same group showed that only bilateral carotid ablation reduced blood pressure in hypertensive rats (McBryde et al. 2013). Professor Heath first found diseased, enlarged carotid bodies in hypertensive patients at necropsy linked to left ventricular weight in 1970 (Barer, 1994). Leaving a single carotid body seems desirable, to respond to hypoxia, acclimatise to hypoxia of altitude or disease, but an intact carotid body would probably also preserve the speed of ventilatory responses to the onset of exercise, (Wasserman et al. 1975), linked to oscillations in arterial with each breath (Band et al. 1980), which modulate chemoreceptor firing (Band et al. 1978), and are altered by the $P_{CO_2}$ timing of pulses of $CO_2$ added to the inspire at sea level and especially after high altitude exposure on Everest (Collier et al. 2008). In the study of Collier et al. dynamic chemosensitivity to $P_{CO_2}$ was only demonstrable in mild exercise, not at rest, but the increased carotid body drive in arterial hypertension might generate dynamic chemoreceptiveness at rest. An eminent mentor of one of our co-authors once described this as ‘dinosaur science’. If so, we now find ourselves in a rather wonderful ‘Jurassic Park’ of integrative physiology, mixing the old and the new. Watch out for ripples in the water.

References


Additional information

Competing interests
None declared.
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Resistant hypertension treatments – one size does not fit all

Melvin Lobo (Consultant Physician and Hon. Senior Lecturer), M. Saxena, T. Brier and V. Kapil
William Harvey Research Institute and Barts NIHR Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK

The emergence of novel interventional sympathomodulatory treatments for resistant hypertension (RHTN) highlights the need for accessible clinical tests to better phenotype the hypertensive state and identify predictors of response which would enable best use of these invasive technologies. Whilst heterogeneity in antihypertensive drug responses is the norm, interventional device-based therapy of hypertension is vastly more expensive and has inherent risk: ultimately the price for being a non-responder may be too costly (Bisognano et al. 2011; Persu et al. 2014b).

Importantly, RHTN may not always be fundamentally due to elevated sympathetic tone and this is reflected in heterogeneous responses to renal sympathectomy (Persu et al. 2014a) and baroreflex activation (Bisognano et al. 2011). Indeed, mechanical large-artery stiffness is increasingly recognized as critical in the development of the isolated systolic hypertensive phenotype (Mitchell, 2014) that is most commonly exhibited in RHTN (Mancia & Grassi, 2002) for which sympathomodulation may not offer a significant BP lowering...
effect. Another novel interventional treatment which creates a fixed-calibre iliac arterio-venous anastomosis looks promising in the management of RHTN due to a non-compliant circulation (Burchell et al. 2014). Phenotyping of the RHTN state should therefore include both assessment of regional/whole body sympathetic tone and haemodynamic factors including arterial stiffness. The debate over which technique for controlling RHTN is therefore redundant – no single intervention is likely to be a panacea. The development of a cadre of interventional technologies coupled to detailed phenotyping in RHTN should facilitate the appropriate selection (or not) of targeted, pathophysiology-specific therapies.

References


Additional information

Competing interests

Dr M. Lobo is on the speaker bureau for St Jude Medical, and is a consultant to ROX Medical and St Jude Medical. Dr M. Saxena, Dr T. Brier and Dr V. Kapil have no competing interests to declare. Published October 29, 2014

Which technique for controlling resistant hypertension? Patient selection will be a key

Michael J. Joyner (MD)

Department of Anesthesiology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA

A key question for device or ablation therapy to therapeutically modulate sympathetic outflow in hypertension is which patients are candidates for such therapy (Joyner, 2014). This is important because of the impressive but inconsistent results with the approaches that are currently under study. In this context, so-called autonomic support of blood pressure varies widely and when powerful ganglionic blocking drugs are given to middle-aged and older humans the fall in blood pressure caused by these drugs varies (Jones et al. 2001; Barnes et al. 2014). Importantly, the fall in blood pressure is inversely proportional to markers of resting efferent vasoconstrictor sympathetic outflow and older observations suggest similar variability in hypertensive patients (Korner et al. 1973). Thus while many patients with hard to treat high blood pressure likely have high levels of ‘sympathetic’ tone driving their hypertension, at least some do not. Current techniques like microneurography, infusions of ganglionic blocking drugs, or use of catecholamine spillover measurements to assess sympathetic tone in humans are complex and not ideal for routine clinical testing. If simpler techniques to determine which patients have high sympathetic tone can be developed, perhaps device or ablation therapy to treat high blood pressure can become more targeted with more consistent results in clinical trials.

References


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the inhibition of sympathetic over-activity seen in patients with CKD can theoretically be renoprotective. In this context, the full utility of RNA in human subjects with renal end-points needs further evaluation.

References


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Which technique to control resistant hypertension? Focus on the patient

John S. Floras

University Health Network and Mount Sinai Hospital Division of Cardiology, University of Toronto, Ontario, Canada

The accomplished authors of all three viewpoints provide cogent and sincere advocacy, backed by experimental evidence, for their respective device-based approaches to the control of resistant hypertension (Jordan, 2014; Schlaich et al. 2014; Ratcliffe et al. 2014). The irony of this paternalistic debate is the absence of the patient’s voice.

In our institution’s experience, 43 patients of 105 referred for renal denervation before the SYMPPLICITY HTN-3 results (Bhatt et al. 2014) were announced truly had drug-resistant primary hypertension following investigation and adjustment of therapy and also met the manufacturer’s renal anatomical criteria for efficacy and safety, yet of these 15 declined when the procedure was offered. In the almost 3 years that it has been approved for research purposes in our institution, no patient has consented to carotid baroreceptor nerve stimulation. We anticipate comparable consultant and patient resistance to similarly perceived brash interventions, such as chemoreceptor denervation. In our view, none of the proposed interventions will alter substantially clinical practice in North America without first establishing randomized clinical trial evidence, persuasive to both patient and physician, predicated on a validated, inexpensive, and generally available biomarker predictive of efficacy.

It is similarly ironic that we have already at our disposal yet generally ignore a much more effective technique for controlling drug-resistant hypertension. This requires neither expensive proprietary devices nor costly hospital resources nor lavish professional procedural reimbursement. It obviates, instead, through the investment of time, the cultivation of trust, and the adoption of tested strategies, modification of both patient behaviour to achieve optimal adherence and physician behaviour to ensure accurate phenotyping and optimal prescription.

References


Additional information

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None declared.

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The need for physiological evaluation to determine the ideal individual intervention to reduce unresponsive hypertension

M. K. Stickland (Associate Professor and Heart & Stroke New Investigator).

Department of Medicine, University of Alberta and G. F. MacDonald Centre for Lung Health, Edmonton, Alberta, Canada

The three research groups provide a nicely balanced evaluation of their respective approaches to a potential treatment for resistant hypertension (Jordan, 2014, Ratcliffe et al. 2014, Schlaich et al. 2014). All authors agree that a ‘silver bullet’ intervention to cure unresponsive hypertension is unlikely. As pointed out by Dr Jordan (Jordan, 2014), there may be important pathophysiological reasons why a certain intervention may not be successful. To me, this is where physiologists can help make important contributions to the area. As one example, there is a high prevalence of unrecognized sleep apnoea in drug-resistant hypertension (Logan et al. 2001), and yet very few of the clinical hypertensive trials have historically objectively tested for sleep apnoea, which is important considering some of the newer interventions may themselves impact sleep apnoea (Witkowski et al. 2011). Our laboratory continues to be interested in the role of the carotid chemoreceptor in autonomic and cardiovascular function. Lately we have been testing all participants for sleep apnoea using an overnight sleep monitoring system, and the prevalence of undiagnosed sleep
apnoea in both well-managed patients, as well as in asymptomatic ‘apparently healthy’ non-obese controls was surprising. As suggested by Ratcliffe et al. (2014), clinical phenotyping is likely needed prior to entry into future well-controlled studies. To me, clinical/physiological phenotyping, which would likely include careful evaluation of potential mechanism(s) for the autonomic or vascular dysfunction as well as thorough evaluation of baroreceptor, chemoreceptor and renal function, is vital as we seek to determine the ideal individual intervention to treat unresponsive hypertension.

References


Additional information

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CrossTalk consensus view: Which technique for controlling resistant hypertension?

Peter O. O. Julu1,2,3,4 (Specialist Autonomic Neurophysiologist and Consultant Physician), Mussadiq Shah1,4, Robert S. Delamont1, David J. Collier1, Chris Wolff3, Manish Saxena1, Tim Brier1, Luke Holdsworth1 and Melvin D. Lobo1

1Hypertension Research, Barts Cardiovascular Biomedical Research Unit, William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, UK
2Division of Brain Science, Department of Medicine, Imperial College London, UK
3Autonomic Neurophysiology Unit, Swedish National Rett Center, Froson, Sweden
4Neuroscience Department, Breakspear Medical Group, Henel Hempstead, UK
5Department of Neurology, King’s College Hospital NHS Foundation Trust, Denmark Hill, London, UK

The golden rule of thumb in clinical medicine is to treat the cause of a disease. Presenting signs and symptoms are usually ameliorated to bearable levels while waiting for the objective treatments to take effect. Hypertension has been the exception to this golden rule for a long time because the amelioration of the presenting sign is the only clinical endeavour in most cases. The consensus view in this CrossTalk is that resistant hypertension (RH) is a presenting sign of autonomic dysregulation or dysautonomia. Target-organ-oriented treatments of RH are unanimously recommended in this CrossTalk. This unique consensus means the causes of RH are diverse and may be target-organ specific. Clinical autonomic neurophysiology to date permits target-organ-oriented assessment of dysautonomia (Julu et al. 1997; Low et al. 2013). We can now quantify the cardiodepressor and vasodepressor activities of the carotid sinus separately and discretely (Julu et al. 1997). We can also quantify the sympathetic efferent function in the splanchnic vascular bed (Stewart & Montgomery, 2005; Duttoit et al. 2009). We can measure the partial pressures of oxygen and carbon dioxide simultaneously in peripheral tissues and correlate the levels with respiration, blood pressure (Julu & Witt-Engerström, 2005) and with brain function (Julu et al. 2013). All these are non-invasive investigations, which can be undertaken in outpatient settings. Therefore the real question is not ‘which technique for controlling RH’, but rather to identify the mechanisms of a specific RH and to rein it back to the golden clinical rule of treating the cause using appropriate techniques.

References


Additional information

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The carotid body as the orchestra conductor in hypertension

Rodrigo Del Río1 (Assistant Professor) and Harold D. Schultz2 (Professor)

1Laboratory of Cardiorespiratory Control, Universidad Autónoma de Chile, Chile
2Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, USA

A major challenge in the development of novel treatments intended to improve blood pressure control in hypertension is to establish an integrative tool that helps reduce the blood pressure in the long term. Renal denervation has been proposed as a suitable intervention to decrease blood pressure in resistant hypertension (Schlaich et al. 2014). In addition, carotid sinus stimulation also showed promising results in reducing blood pressure (Jordon, 2014). Furthermore, McBryde et al. 2013, showed in elegant experiments that denervation of the carotid body (CB) is an effective tool...
to normalize blood pressure during the progression of hypertension.

Interestingly, all three approaches are much more interrelated than one might assume. It is well known that the CB chemoreflex activates sympathetic discharges to key organs involved in the development, progression and maintenance of high blood pressure (Ratcliffe et al. 2014). An important component to this effect is increased entrainment of sympathetic outflow to the respiratory cycle. In addition, the CB chemoreflex also facilitates sympathetic outflow by acting centrally to inhibit the baroreflex and to enhance excitatory sympathetic afferent reflexes from peripheral organs. Thus, denervation of the CBs reduces sympathetic outflow by an integrated central mechanism that involves:

(1) silencing of central CB chemoreflex pathways linked to sympathetic outflow; and
(2) a central resetting of baroreceptor and visceral afferent reflexes, including possibly that from the kidney. In experimental heart failure, another sympatho-mediated disease, CB denervation markedly decreases neuronal activation in brainstem areas related to sympathetic control and significantly reduces sympathetic influences to the heart (Del Rio et al. 2013). Therefore, CB denervation should be seen as an integrative tool to normalize autonomic balance due to its important central effects not only on respiratory–sympathetic coupling but also central resetting of other reflexes affecting autonomic control.

References


Additional information

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