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REVIEW

Clinical update

Interventional procedures and future drug therapy for hypertension

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Hypertension management poses a major challenge to clinicians globally once non-drug (lifestyle) measures have failed to control blood pressure (BP). Although drug treatment strategies to lower BP are well described, poor control rates of hypertension, even in the first world, suggest that more needs to be done to surmount the problem. A major issue is non-adherence to antihypertensive drugs, which is caused in part by drug intolerance due to side effects. More effective antihypertensive drugs are therefore required which have excellent tolerability and safety profiles in addition to being efficacious. For those patients who either do not tolerate or wish to take medication for hypertension or in whom BP control is not attained despite multiple antihypertensives, a novel class of interventional procedures to manage hypertension has emerged. While most of these target various aspects of the sympathetic nervous system regulation of BP, an additional procedure is now available, which addresses mechanical aspects of the circulation. Most of these new devices are supported by early and encouraging evidence for both safety and efficacy, although it is clear that more rigorous randomized controlled trial data will be essential before any of the technologies can be adopted as a standard of care.

Keywords Hypertension • Sympathetic nervous system • Renal denervation • Baroreflex activation • Arteriovenous anastomosis • Drug therapy

Introduction

Hypertension affects >1 billion people globally and is the number one risk factor for cardiovascular morbidity and mortality.[1] Although many different classes of antihypertensive drug are available, side effects of drugs resulting in variable patient adherence are problematic.[2,3] Additional drug therapies are therefore needed with excellent tolerability profiles in addition to proven safety and efficacy. Moreover, for those patients who either do not wish to take drugs lifelong or who experience disabling adverse effects from drug therapy, non-pharmacological measures over and above lifestyle modification are urgently required. We consider the newly emerging field of interventional procedures for hypertension and also what is on the horizon for novel pharmacological approaches to improve BP control.

Part I: interventional procedures for hypertension

An increasing number of technologies are in the pipeline at various stages of development (see *Table 1*), but this review will restrict itself to considering those therapies for which human feasibility studies have been published (see *Figure 1*). Regardless of which device therapy is being considered, it is important to recognize the need for the involvement of hypertension specialists in the optimal work up and management of patients to enable appropriate selection for therapy.[4–8] Moreover, multidisciplinary collaboration among hypertension specialists, interventionalists, and physiologists will be essential for the design, execution, and analysis of forthcoming studies.

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Table 1 Novel device technologies for treatment of hypertension

Technology	Mode of action	Stage of development	Limitations
Renal sympathetic denervation Ablation catheters and generators available from several manufacturers including Medtronic, St Jude Medical, Boston Scientific, Terumo, and Verve Medical	Sympathomodulatory—results in destruction of renal afferent and efferent sympathetic nerves and BP reduction through mechanisms that remain unclear in human hypertension	CE Mark approval for hypertension for most catheters A variety of catheters/platforms now available includes: Radiofrequency ablation, ultrasound ablation, chemical ablation, and cryoablation using balloon/non-balloon and irrigated catheters	Lack of markers of procedural success Inability to screen for increased renal nerve signalling prevents identification of best responders Damage to renal artery from endovascular approach using thermal energy
Baroreflex activation therapy Barostim neo™ (CVRx Inc, Minneapolis, MN, USA)	Sympathomodulatory: unilateral electrical field stimulation of the carotid sinus stimulates the baroreflex and down-regulates sympathetic outflow while increasing parasympathetic tone	CE Mark approval for hypertension Pivotal study published with the first-generation device[58] Small proof of concept study with the second-generation device[61]	Open loop system lacks feedback mechanism Exceedingly high cost Implantable generator must be replaced at end of battery life (currently 3 years)
Baroreceptor amplification therapy Mobius HD™ (Vascular Dynamics, Mountain View, CA, USA)	Sympathomodulatory: dramatic increase in carotid bulb strain causes durable amplification of baroreceptor feedback and BP reduction	European and US studies now enrolling Case report and early report from first-in-man study published[127,128]	Concerns over instrumentation of the carotid artery, risks of distal embolization Open loop system with no feedback mechanism
Central iliac AV anastomosis ROX AV coupler™ (ROX Medical, San Clemente, CA, USA)	Targets mechanical aspects of the circulation Lowers BP through reduction in effective arterial volume and systemic vascular resistance	CE Mark approval for hypertension Small randomized controlled study in resistant hypertension published[68] and US IDE study with sham control is planned to start enrolling in 2016	30% incidence of ipsilateral venous stenosis Risk of high output cardiac states not known No long-term safety data
Carotid body ablation Cibiem Carotid Body Modulation System™ (Cibiem, Los Altos, CA, USA)	Sympathomodulatory: unilateral carotid body ablation reduces sympathetic vasomotor tone without affecting respiratory drive	Proof of concept study using unilateral surgical excision in resistant hypertension[74] Endovascular ablation planned using novel catheter-based system	Only appears effective in those with high carotid body tone. Screening for this will be essential Endovascular approach is complicated by the difficulty of accessing the target and risks to important adjacent structures
Deep brain stimulation Activa Neurostimulator, (Medtronic Inc., Minneapolis, MN, USA) Vercise™ DBS System (Boston Scientific, Marlborough, MA, USA)	Sympathomodulatory: electrical field stimulation of the dorsal and ventrolateral periaqueductal grey region within the midbrain reduces BP through mechanisms that are not clearly defined in human hypertension	The technology was primarily developed for management of movement disorders and chronic pain syndromes.[129] Isolated reports of BP-lowering independent of pain control[130,131]	Limited efficacy/safety data High costs of therapy Open loop system Frequent generator recharging required
Vagal nerve stimulation CardioFIT™ Systems (BioControl Medical, Yehud, Israel) Precision™ System, (GUIDANT Europe/Boston Scientific)	Sympathomodulatory—unilateral vagal nerve stimulation restores vagal tone and improves sympathovagal balance	Under investigation for use in heart failure and hypertension. Animal data only for hypertension indication[132]	Inability to selectively target nerve fibres to avoid bradycardia and bradypnoea
Median nerve stimulation Subcutaneous Neuromodulation System (Valencia Technologies, Valencia, CA, USA)	Sympathomodulatory—subcutaneous unilateral implantation of a coin-sized device (in a 20-min office procedure) causing electrical stimulation of the median nerve and subsequent down-regulation of sympathetic outflow	A double-blinded study in 29 patients has shown reduction in ambulatory BP at 3 (9.2 mmHg) and 6 (18.9 mmHg) months http://valenciatechnologies.com/clinicaltrial/	No published randomized controlled data[133]

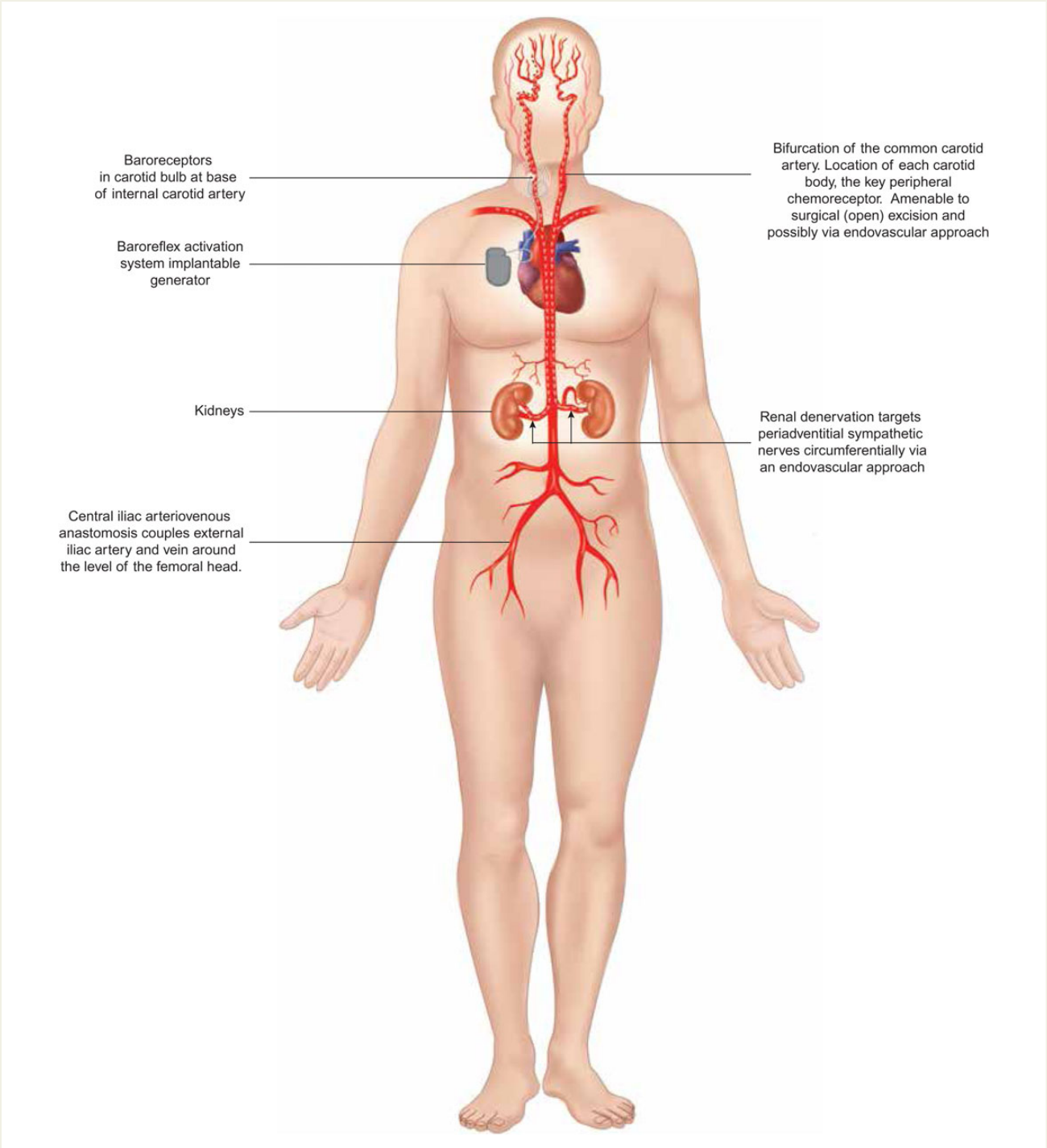

Figure 1 Interventional procedures for hypertension.

Renal sympathetic denervation

Rationale

Renal sympathetic nerves are important in the initiation of hypertension, and maintenance of the hypertensive state and interventions in animal models to abrogate renal sympathetic signalling prevent both the development of hypertension and lower BP.[9,10] Increased renal sympathetic outflow, demonstrated in human hypertension, suggests that renal sympathetic nerves, conveniently located in a peri-arterial distribution, might be an attractive target for the treatment of hypertension.

Evidence to date

Selective endovascular renal sympathectomy has been available for the past 5 years using catheter-based renal ablation with radiofrequency (RF) energy. The Symplicity HTN-1 feasibility study ignited

interest in the field after demonstrating substantial and safe office BP reduction of 27/17 mmHg in patients with resistant hypertension (RHTN) after 12 months of follow-up.[11] The subsequent open label randomized non-sham-controlled Symplicity HTN-2 study also generated enormous publicity in the medical and lay press after demonstrating striking office BP reduction of 33/11 mmHg in RHTN patients treated with renal denervation (RDN) compared with control patients ($P < 0.001$).[12] However, ambulatory BP monitoring, performed in only half the patients, showed less impressive reduction than office BP in the RDN group (11/7 mmHg).

Heterogeneity of response to RDN was beginning to emerge in these earliest studies and continued to be a feature of numerous small, uncontrolled studies of RDN thereafter.[13] Criticisms of the accumulating RDN dataset iterated several common themes including sub-optimal work up for secondary hypertension, study bias due to lack of blinded BP endpoints, lack of sham-controlled procedure and inadequacy of follow-up.[14] To address these and other valid issues, the Symplicity HTN-3 study was undertaken in the USA and published its report in early 2014 to the surprise of many clinicians and those in the medical device industry.[15] This study, the largest of RDN to date, failed to demonstrate a difference in office and ambulatory BP lowering between patients treated with RDN and the sham (renal angiogram)-controlled group and thus failed its primary and secondary efficacy endpoints, although crucially the RDN procedure was deemed to be safe. Substantial limitations of this study have been subsequently identified by the investigators and have been the subject of extensive commentary.[4,16,17] These include important differences in baseline medication usage between the groups, unstable medications at baseline and 40% medication changes in both groups throughout the study. Most worryingly, only 19 of 364 patients (5%) treated with RDN actually received bilateral ablation in all four quadrants of the renal artery. Not surprisingly, those that did receive per-protocol ablation therapy exhibited the greatest reductions in office, home, and ambulatory systolic BP (-24.3, -9.0, and -10.3 mmHg, respectively).[17]

Prior to Symplicity HTN-3 several thousand patients had been treated worldwide, mostly using the first-generation single-electrode Symplicity catheter. Most of these patients were treated as a standard of care rather than in clinical trials, although data for some was captured in the Global Symplicity Registry. The first report from this dataset indicates that RDN is a safe and effective treatment for RHTN: 6 months following RDN, the reductions in office and 24-h systolic BPs were 12 and 7 mmHg, respectively, for all 998 patients (baseline office BP 164 mmHg) and 20 and 9 mmHg for 323 patients with severe hypertension (baseline office BP 179 mmHg), respectively ($P <$ 0.001 for all responses).[18] Similarly, the UK Renal Denervation Affiliation has reported large reductions in office and ambulatory BP (22/9 and 12/7 mmHg, respectively, $P < 0.001$ for both) in 253 patients with severe hypertension (baseline office BP 185/102 mmHg) treated according to strict criteria with five different RDN catheters and suggests that real world application of RDN is successful when done per protocol.[19]

Despite the widespread adoption of RDN soon after the initial studies were published, there is a striking paucity of randomized controlled trial (RCT) data for RDN and the majority of the studies that exist are small in size with only 180 patients actively treated with RDN (excluding flawed Simplicity HTN-3), substantially less than the registries described earlier.[12,15,20–24] A recent meta-analysis of these studies indicates that among all 588 patients treated with RDN in RCTs, there were heterogeneous effects for office and ambulatory BP which were not significantly reduced compared with control (see *Figure 2*).[25]

Current technologies

Current approaches to RDN increasingly make use of multi-electrode catheters for RF ablation and irrigated balloon catheters for ultrasound (US) ablation.[26–29] A separate class of catheters makes us of microinjection of neurotoxin (e.g. alcohol) to chemically ablate renal nerves and has the potential advantage of facilitating deeper nerve injury whilst avoiding endothelial damage.[30] Separately, a non-vascular catheter-based technology deploys a transurethral approach to ablate the renal pelvis which is richly innervated with afferent fibres and could be an alternative for patients with bleeding disorders or renal artery anatomy that is unsuitable for current endovascular ablation catheters.[31] A wholly non-invasive US platform (Surround Sound™, Kona Medical) that targets the distal renal artery and bifurcation using advanced Doppler imaging is currently in clinical trials in Europe with a US pivotal study planned to start recruiting in 2016.

Concerns for the future

Is it acceptable to injure the renal artery to access a remote target?

Balloon catheterization of the renal artery and thermal energy arising during RF/US ablation result in acute vascular injury. Using optical coherence tomography, it was shown that diffuse vasospasm, oedema, and thrombus formation immediately follow single- and multi-electrode RDN with more thrombus noted with the latter.[32] In addition, it was demonstrated that no-balloon and balloon catheters result in different patterns of thermal injury with dissection occurring more commonly with balloon treatment.[33]

The long-term consequences of renal artery injury following RDN are not established but it is worrying to see increasing reports of renal artery stenosis post-RDN which represents only the clinically manifest cases presenting with acute BP elevation.[34–36]

How can the renal sympathetic nerves be precisely targeted?

Knowledge of human renal artery microanatomy was surprisingly limited until recently. However, a small human cadaveric study showed that these nerves lie in closest proximity to the lumen in the anterior and posterior quadrants of the distal renal artery, although at lesser density compared with proximally.[37] In a porcine model, distal main renal artery plus branch ablation resulted in greater nerve destruction than proximal ablation alone and that increasing numbers of ablations are less critical than distal lesion placement.[38,39]

The importance of the renal artery microenvironment

The microenvironment of the renal artery is vastly different to the myocardium wherein much experience of ablation platforms resides: ventrally located heat sinks (e.g. veins) act to disperse thermal energy while dorsally located fibrous muscle sheaths can increase the extent of ablation.[40,41] Blood pressure reduction post-RDN is exquisitely dependent upon the extent of nerve injury and ablation,

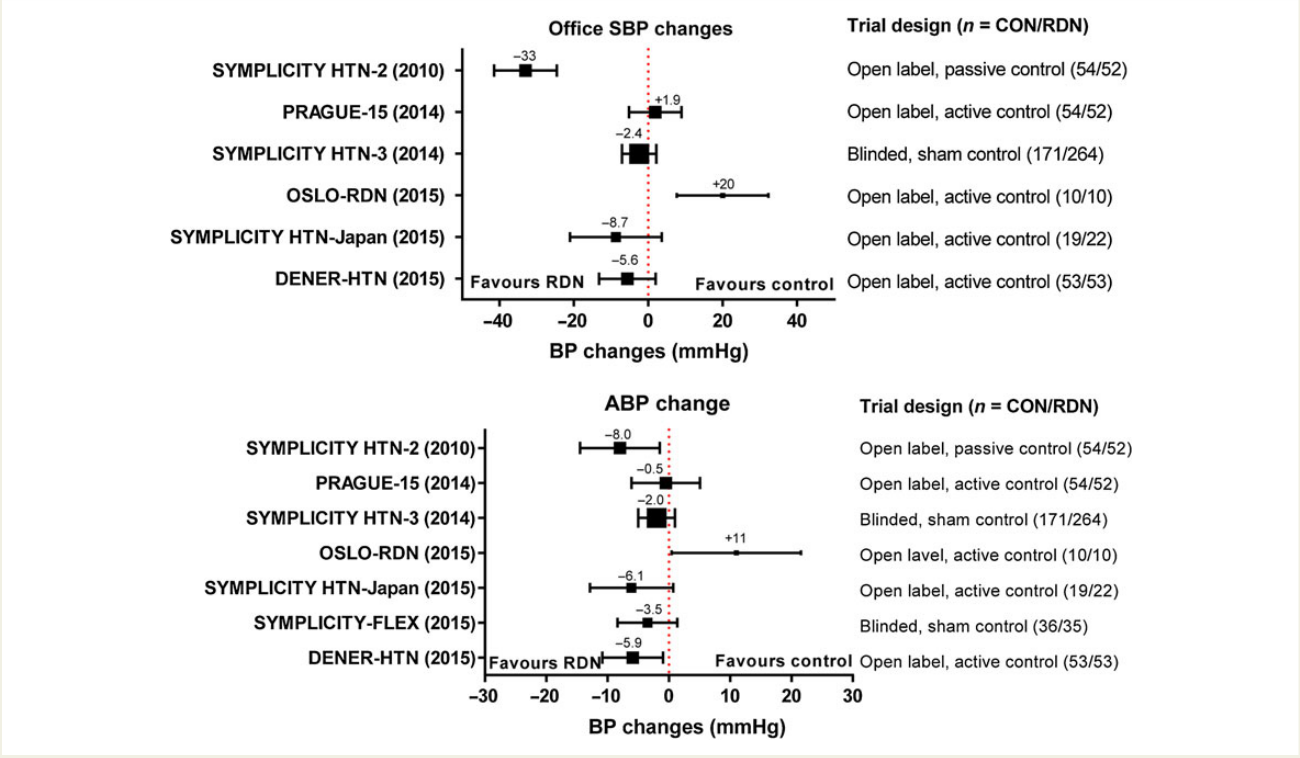

Figure 2 Randomized controlled trials of renal denervation SBP, systolic BP; ABP, ambulatory BP. Image supplied courtesy of Dr K Chan.

which is largely dictated by the local tissue anatomy; irrigated multi-electrode catheters might therefore optimize ablation efficacy.[40]

Is nerve regrowth an issue or potential future concern?

Although re-innervation following RDN might occur, durable office BP reduction for up to 36 months was shown in the early Symplicity cohorts.[42,43] Clinically, significant re-innervation has now been demonstrated in a pre-clinical sheep model: the occurrence of functional re-innervation in humans post-RDN has not been identified, although the transplanted human kidney seems not to demonstrate this.[44,45]

Are populations identifiable where renal sympathetic activity strikingly contributes (or not) to hypertension?

Beyond technical failure, the fact that renal nerves do not contribute to hypertension in all patients remains a potential clinical issue.[46] Esler identified that with increasing age, renal norepinephrine spillover falls, suggesting that mechanisms other than sympathetic drive contribute to hypertension in the older adult.[47] Ewen and colleagues reported diminishing RDN treatment effect in patients with isolated systolic hypertension, suggesting that patients with structural hypertension may not be ideal candidates for RDN therapy.[48] Thus, ideal patient selection must identify if renal sympathetic nerves contribute to systemic hypertension before committing patients to the therapy.

Future directions

Experts are in joint agreement over the need for the field of RDN therapy to build a new clinical basis with additional RCTs, although there is debate over the requirement for sham control.[5,6,49] Three strategies to further identify ideal patients, enhance technical success, and optimize patient and investigator blinding have evolved:

(i) Experimenting in drug naïve patients to eliminate the confounding effects of occult changes in pharmaceutical compliance on outcomes.
(ii) Development of tools to identify patients with significant contribution of renal sympathetic nerves to hypertension, and which enable documentation of procedural and technical success.
(iii) Requiring the use of ambulatory BP as an endpoint to eliminate the potential contribution of physician measurement bias on the outcome.

At this time, there is no obvious solution to nullify the impact of patient awareness of home BP on their pharmaceutical compliance and clinical behaviours.

Baroreflex activation therapy

Rationale

Arterial baroreceptors located along the carotid sinus and aortic arch are stimulated in response to arterial BP elevation and reflexively send afferent nerve impulses into the nucleus tractus solitarius in the central nervous system. This in turn leads to decreased sympathetic efferent output and BP lowering as well as increased parasympathetic outflow resulting in bradycardia.[50,51]

More than half a century ago studies in canines and in hypertensive humans demonstrated that electrical activation of the carotid

baroreflex resulted in BP lowering.[52,53] However, further development of the therapy was severely hampered by technological limitations and also surgical issues such as difficult implantation, unintended nerve, and muscle stimulation and nerve injuries.[54,55]

Procedure

Baroreflex activation therapy delivers electrical field stimulation at the carotid sinus to lower BP. The first-generation Rheos™ system utilized an implantable pulse generator and bipolar electrodes which were surgically attached to the carotid sinus under general anaesthesia. Subsequently, a second-generation device (Barostim Neo™) has replaced Rheos and encompasses a single unipolar electrode and miniaturized generator with improved battery life (see *Figure 1*).[56] The procedure can now be done under conscious sedation with a much improved safety profile.

Clinical trial data

The Rheos device was initially evaluated in a feasibility study in 45 patients with RHTN which showed an average office BP reduction of 21/12 mmHg at 3 months and 33/22 mmHg at 2 years.[57] Subsequently, in the Rheos Pivotal Trial,[58] 265 patients were randomized in a 2:1 fashion to early or delayed device activation (1 or 6 months post-implantation, respectively). There was no significant difference between groups in the primary efficacy end point of at least 10 mmHg drop in systolic BP. The study also failed to meet its early safety endpoint with 9% of patients developing transient (4.4%) or permanent (4.8%) facial nerve injury. Open label, non-randomized follow-up of the whole cohort reported that office systolic BP reduction of >30 mmHg was sustained up to 53 months with no important safety concerns.[59] Subgroup analysis of the Rheos Pivotal Trial showed that most patients achieved target BP with unilateral therapy.[60]

A preliminary study with Barostim neo™ system in 30 patients with RHTN demonstrated office BP reduction of 26.0/12.4 mmHg at 6 months from a baseline of 171.7/99.5 mmHg. Importantly, there were shorter implantation and hospitalization times, as well as less immediate procedure-related complications compared with the first-generation system and no reports of either temporary or permanent facial nerve injury.[61]

Future directions

The Barostim Neo™ system has CE Mark approval for the treatment of RHTN and for heart failure. The manufacturer is currently undertaking the Barostim Hypertension Pivotal Trial (clinicaltrials.gov: NCT01679132) and a heart failure study (clinicaltrials.gov: NCT00718939). The therapy is costly (in excess of €20 000 for the hardware alone) and further efficacy/safety data for the Barostim Neo device will be required to better define the role of this therapy in both hypertension and heart failure.

Central iliac arteriovenous anastomosis

Rationale and mechanism of action

This novel approach is thought to principally address mechanical aspects of the circulation as opposed to primarily targeting the SNS. The central iliac arteriovenous (AV) anastomosis creates a fixed calibre conduit between the proximal arterial and low resistance venous circulation, which helps to restore the Windkessel function of the central circulation and thus providing a unique opportunity for improving proximal vascular compliance.[62–64] The anastomosis causes an immediate, significant reduction of BP, and systemic vascular resistance. The mechanism is related to the immediate reduction of effective arterial volume, vascular resistance, and buffering the contribution of reflected wave forms. Some sympathomodulatory effects are likely: by increasing venous oxygenation and right heart stretch through increased pre-load.[62]

Procedure

A 4-mm AV anastomosis between the external iliac artery and vein is created using a nitinol stent-like device (ROX AV coupler) in a 40-min catheterization laboratory procedure under fluoroscopic guidance (see *Figure 3*A).[65] In contrast to an RDN procedure, AV coupler deployment is verifiable and reversible if required, resulting in

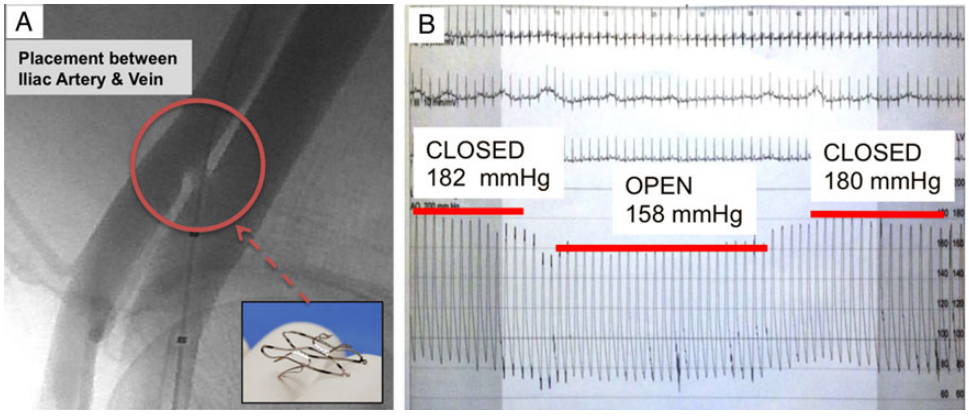

Figure 3 (*A*) ROX device and placement under fluoroscopic guidance. (*B*) Immediate, verifiable BP reduction with coupler opening and reversal with closure. (images reproduced with permission of ROX Medical).

the diversion of a calibrated amount of arterial blood (0.8–1 L/min) into the proximal large capacitance venous circuit (see *Figure 3B*). The immediate reduction in both systolic and diastolic BP obviates any contribution from placebo/Hawthorne effects.[62,63]

Clinical data and safety considerations

Initially, the device was studied in patients with severe chronic obstructive pulmonary disease (COPD), with moderate improvement in 6 min walking distance and no safety signal.[66] A subsequent open label study of 24 patients with COPD and mild hypertension demonstrated a significant reduction in office BP from 145/86 to 132/67 mmHg at 12 months leading to a repurposing of the device for the hypertension indication.[67]

In the ROX CONTROL HTN trial,[68] 83 patients with RHTN were randomized in a 1:1 ratio to receive standard care or insertion of AV coupler with standard care. At 6 months, office BP and ambulatory BP were reduced by 27/20 and 14/14 mmHg, respectively, in the coupler group ($P < 0.0001$ for all changes) while in the control group, there was no significant change in either. In a subgroup of patients who had prior RDN, there was highly significant office and ambulatory BP reduction (34/22 and 12/15 mmHg, respectively) in the coupler group at 6 months with no significant change in the control group for either. This suggests that AV coupler therapy may be of benefit in cases where sympathomodulation has failed.[69]

Ipsilateral venous stenosis was seen at ~6 months post-coupler insertion in 29% of the patients and this was managed by successfully by venoplasty and/or stenting in all patients. There was a significant reduction in hospitalizations for hypertensive urgencies in the coupler group.[68]

Future directions

Inevitably and mistakenly, the AV coupler is compared with upper limb fistulae for haemodialysis access. Important distinctions are that coupler flow is calibrated and that the anastomosis is not repeatedly punctured for dialysis access. Reassuringly, the anastomosis is fully reversible with a covered stent. To date, there are no reports of high output cardiac failure in treated patients and this has not been previously reported in fistulae of this diameter or in patients with shunt fractions this small.

The coupler is being further evaluated within a global registry study (clinicaltrials.gov: NCT1885390). A sham-controlled US-based IDE trial will begin enrolling in 2016. The immediate very significant reduction of BP and the ability of many patients to appreciate a thrill over the involved groin may reduce the success of sham in treated patients.

Carotid body ablation

Rationale and mechanism of action

Carotid bodies (CBs) are peripheral chemoreceptors that regulate respiratory minute ventilation and sympathetic tone in response to stimuli such as hypoxia, hypercapnia, hypoglycaemia, and acidosis.[70,71] In both animal models and humans, increased CB tonicity can lead to hypertension and furthermore reversible inactivation of CB signalling can reduce systemic sympathetic tone in human hypertension and lower BP.[70] In the 1940s, bilateral surgical resection of the CB in humans was commonly undertaken for asthma.[72] The procedure was safe but did not lead to significant benefits in ventilatory parameters. However, in a subset of hypertensive patients, average systolic BP was lowered by 40 mmHg at 5 days post-operatively and this reduction was maintained out to 6 months.[73]

Clinical trial data and future perspectives

A proof of concept study in patients with RHTN who had unilateral CB ablation has demonstrated significant, durable office BP reduction of 23/12 mmHg at 6 months post-operatively in patients (8 of 15) with evidence of increased baseline CB activity. Hypoxic ventilatory drive was not disrupted and no serious adverse events were observed at up to 12 months of follow-up.[74] Unilateral endovascular CB ablation for RHTN using the Cibiem Carotid Body Modulation System™ is currently being evaluated (clinicaltrials.gov: NCT02099851).

Part II: future drug therapy for hypertension

The challenges for new antihypertensive drug approaches are as follows:

- to demonstrate meaningful BP reduction
- to identify a population of hypertensive patients in whom a new drug could provide benefit
- to modify hard outcomes in clinical trials meeting modern methodological standards.

This section will examine the main target of new antihypertensive drugs (see *Table 2*): the results of experimental and clinical trials will be reviewed emphasizing their potential advantages and disadvantages.

Old systems revisited: the renin–angiotensin–aldosterone system

(*Figure 4*)

Aldosterone receptor antagonism

Rationale

Aldosterone is a mineralocorticoid synthetized from 11-deoxycorticosterone, though the action of aldosterone synthase encoded by the CYP11B2 gene.[75] This hormone binds to the mineralocorticoid receptor (MR) and leads to cardiac effects (myocardial hypertrophy and fibrosis) vascular changes (mediated by an increase in oxidative stress and decrease in nitric oxide bioavailability) and renal effects (sodium plus water retention).[76]

Clinical trial data

Currently, two novel pharmacological strategies target this pathway: aldosterone synthase inhibition and new non-steroidal MR antagonists (MRA). New MRA such as eplerenone do not have the anti-androgenic, partial oestrogen receptor agonist effects of spironolactone. However, eplerenone has a short half-life and is less potent than spironolactone and has never been formally established as an antihypertensive therapy.[77]

A newly available non-steroidal MRA (finerenone) has been described as more selective than spironolactone, and with greater affinity than eplerenone, for the MR.[78] Despite these properties,

Table 2 Drugs in development for hypertension

Drugs	Pharmacodynamic effect	Phase of clinical trial	Effect on BP
Finerenone	MRA	Phase 2 B (heart failure)	None
LCI699	ASI	Phase 2	Minor BP reduction
Rh ACE2	ACE2 activator	Phase 1	No effect on BP
RB150	Aminopeptidase A inhibitor	Phase 1	Safe, Phase 2 study planned in hypertension
LCZ696	Dual ARB–neprilysin inhibitor	Phase 3, available for HF	Reduced office SBP and DBP and ABP
Daglutril	Dual ECE–neprilysin inhibitor	Phase 2	Lower BP in patient with diabetes and nephropathy
PL3994	NP A agonist	Phase 2	Reduction in systemic BP
AR9281	Soluble epoxide hydrolase Inhibitor	Phase 2	Ineffective
Vasomera	VIP-Receptor 2 agonist	Phase 2	Safe in Phase 1
AZD1722	Intestinal Na^+/H^+ Exchanger 3 inhibitor	Phase 1	Studies on-going
Etamicastat	DBH inhibitor	Phase 1	Dose-dependent decrease in 24 h ABP
Vaccine	Against Ang II	Phase 2	Significant BP reduction

MRA, mineralocorticoid receptor antagonist; ASI, aldosterone synthase inhibitor; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECE, endothelin-converting enzyme; NP A, natriuretic peptide A; VIP, vasoactive intestinal peptide; DBH, dopamine beta hydroxylase; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABP, ambulatory blood pressure.

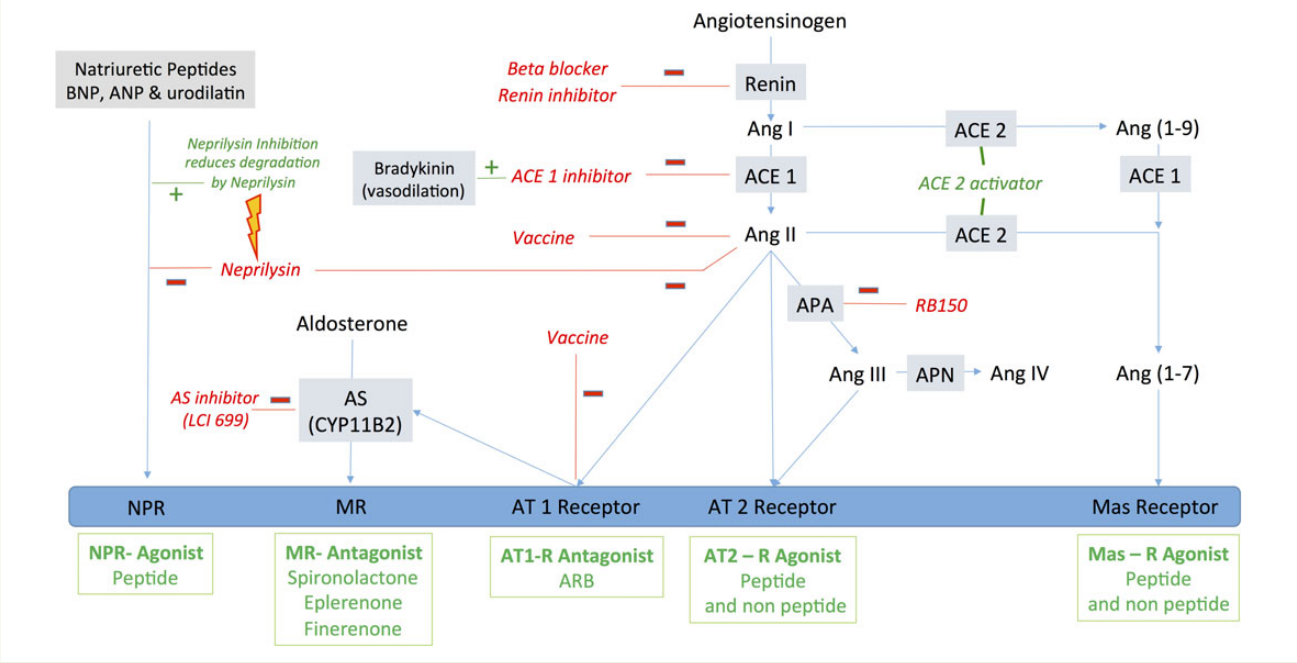

Figure 4 Drugs targeting the renin–angiotensin–aldosterone system. Neprilysin also contributes to breakdown of Angiotensin II and thus Neprilysin inhibition is combined with angiotensin receptor blockade in the ARNI class of drugs (angiotensin receptor neprilysin inhibitor). ACE, angiotensin-converting enzyme; Ang, angiotensin; APA, aminopeptidase A; APN, aminopeptidase N; AS, aldosterone synthase; MR, mineralocorticoid receptor; AT, angiotensin; AT1-R/AT2-R, angiotensin 1-, 2-receptor; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

finerenone, in common with many drugs targeting the renin–angiotensin–aldosterone system (RAAS), has been first tested in heart failure patients with reduced ejection fraction and CKD.[79]

Future directions

This pharmacological approach may be more appropriate for patients with comorbidities (e.g. hypertensive heart failure patients) rather than solely as an antihypertensive.

Inhibition of aldosterone synthesis

Rationale

Blockade of the MR causes reactive increase in RAAS components counteracting the expected benefits from MRA. This partly led to the development of aldosterone synthase inhibitors (ASIs) such as LCI699 which dose-dependently decreases plasma and urine aldosterone concentrations with concomitant increase in plasma renin activity.

Clinical trial data

Up to now, four Phase 2 studies have been performed in hypertensive patients, two showed that in comparison to placebo modest reductions in BP were recorded and when compared with eplerenone results were non-inferior, independent of the dose tested.[80–82] Two additional studies allowed identification of the maximal tolerated dose and safety plus efficacy of LCI699 in comparison to eplerenone as add on therapy in patients with resistant hypertension.[83,84] The results were disappointing with inferior BP-lowering effect compared with eplerenone. The major drawback was lack of selectivity leading to off target effects related to CYP 11B1 inhibition and a significant increase in 11-deoxycorticosterone which can activate the MR and thus limit the beneficial effect of ASI.

Future directions

Currently, the development of ASI as an antihypertensive therapy is on hold. Recent identification of novel compounds namely pyridyl- or isoquinolinyl-substituted indolines and indoles, with greater selectivity for aldosterone synthase and prolonged half-life, has triggered new trials in the field of mineralocorticoid pathway-related cardio-renal disease.[85] The recent conclusion from the PATHWAY 2 trial that Spironolactone was the most effective add-on drug for the treatment of resistant hypertension reinforces the importance of the aldosterone pathway in the pathophysiology of hypertension and extra-renal conditions.[86]

Angiotensin I and II receptors as targets

Rationale

Stimulation of the angiotensin type 2 (AT2) receptor leads to opposite effects from angiotensin type 1 (AT1) receptor stimulation through binding of ligands such as Angiotensin (Ang) II, III, IV, and Ang-(1–7) (see *Figure 1*). Ang-(1–7) produced by angiotensin-converting enzyme 2 (ACE2) from Ang II opposes AT1 receptor-mediated effects via its binding to the Mas receptor, though it also binds to AT2 and even partially to AT1 receptors.[87]

Clinical trial data

Four candidate drugs have been specifically developed to target this pathway, three peptidic agonists and one non-peptidic agonist. Despite the data on AT2 receptor-mediated vasodilation, some of these drugs do not have any effects on BP; some like C21 have pleiotropic effects explaining the observed anti-fibrotic and anti-inflammatory effects.[88,89]

Ang (1–7) has multiple cardioprotective effects but weak vasodilatatory properties making it less suitable as an antihypertensive agent.[90] Similarly, ACE2 stimulation lowers BP but more because of its ability to reduce Ang II concentration than alter production of Ang-(1–7).[91]

Future directions

The lack of BP-lowering effect despite AT2-mediated vasodilation suggests that these therapies will not be developed for hypertensive patients. However, despite weak haemodynamic effects, the ACE2—Ang-(1–7)—Mas receptor axis is potentially a more promising target. The short half-life of Ang-(1–7) and its agonist effect on AT1 receptors at high concentration led to the development of peptidic and non-peptidic drugs, lowering BP in hypertensive animals using the encapsulated form.[92] Clinical trials are needed to assess the benefit–risk ratio of this approach.

Angiotensin as a target

Rationale

At the brain level, the metalloproteinases aminopeptidase A (APA) and aminopeptidase N are, respectively, involved in the metabolism of Ang II and Ang III (a peripheral AT2 agonist but acting centrally as an AT1 ligand) and also Ang IV (see *Figure 4*).[93,94] Ang III binds receptors with affinity for Ang II leading to an increase in BP via direct and indirect activation of the central sympathetic nervous system (through baroreflex inhibition) and also through activation of the arginine–vasopressin pathway.[95]

Experimental trial data

Inhibition of APA by EC33 has been logically identified as a potential target for the management of hypertension.[96] Recently, the orally administered pro-drug RB150, which after crossing the blood–brain barrier is converted to EC33, normalizes BP for several hours through the aforementioned mechanisms of action without affecting systemic RAAS activity suggesting a potential role for the combination of APA inhibitors with peripheral RAAS blockers.

Future directions

The above observations led to a first in man trial confirming the safety of a dose-escalating approach in healthy volunteers paving the way for further exploratory studies in the treatment of hypertension.[97] This central inhibition of the RAAS could provide some particular added value in difficult to control hypertensive patients and possibly those with neurovascular diagnoses.

The renin–angiotensin–aldosterone system and vaccines

Rationale

The development of vaccines targeting the RAAS for the treatment of hypertension is a long running story comprising three major epochs underpinned by the aims to target patients with compliance issues and also to expand hypertension therapy through involvement of a new immunomodulatory pathway.

Clinical trial data

Initial therapies targeting renin, angiotensin, and ACE were associated with autoimmune diseases and subsequent refinement led to a more controlled immunogenic response albeit with conflicting results in term of BP reduction.[98,99] The second phase of development was based on development of a novel immunization agent associated with a significant reduction of BP, predictable adverse events (as seen in other vaccine trials) and with pharmacokinetic data compatible with the need for several injections per year.[100] In the most recent phase, trials have investigated not only new doses and different timing of immunization (utilizing the concept of accelerated immunization) but also novel targets (angiotensin receptors, Ang II) and vectors (virus) identifying that antibody titres, affinities, and type of hypertension (baseline level of BP, severity of the disease) have to be take into account to better inform the development of future vaccine therapy.[100–102]

Future directions

There remain concerns regarding pharmacokinetics and risk management of a vaccine-based approach inhibiting physiological responses to medical emergencies.

New systems explored

Neprilysin inhibition

Rationale

An increase in natriuretic peptides (NPs; atrial/brain/C-type) and urodilatin concentration arises from inhibition of neprilysin, which degrades these peptides and in addition numerous vasoconstrictor peptides.[103] This dual action explains the need for neprilysin inhibitor to be combined with blockade of the RAAS or endothelin-converting enzyme inhibitors (see *Figure 4*).

Clinical trial data

LCZ696 was the first in class angiotensin receptor-neprilysin inhibitor (ARNI) associated with a decrease in BP greater than the BP-lowering effect of valsartan or sacubutril alone.[104] LCZ696 was also shown to safely reduce BP in severely hypertensive Asian patients (office BP > 180/110 mmHg) and was well tolerated.[105] Modest effects on BP led to re-purposing of the drug to the field of heart failure both with and without reduced ejection fraction.

Future directions

Hypertensive patients with reduced ejection fraction-related heart failure could be the patient of choice for LCZ 696 (now Entresto®).[106]

Natriuretic peptide receptor agonism

Rationale

Natriuretic peptide receptor (NPR) agonists (which can reduce BP and lead to cardio and nephroprotective effects) are also being developed as an alternative to NP degradation (*Figure 4*).[107]

Clinical trial data

A subcutaneous dose of an NPR agonist was associated with a significant BP reduction compared with placebo in hypertensive patients (ClincialTrials.gov: NCT00686803). Angiotensin-converting enzyme inhibitors act synergistically and suggest that this approach could be used as an adjunct to therapy for patient with uncontrolled hypertension.

Future directions

Clinical trials with nesiritide, a recombinant form of human B-type NP, infused in patients with advanced heart failure, led to disappointing results including worsening of renal function or heart failure. These mixed results justify further investigation into the utility of targeting the NP system in the setting of hypertension.[108,109]

Vasoactive intestinal peptide as a target

Rationale

Vasoactive intestinal peptide (VIP) is a neuropeptide with vasodilatatory, inotropic, and chronotropic properties.[110,111]

Clinical trial data

This peptide binds to both VPAC1 and VPAC2 receptors, leading, respectively, to gastrointestinal side effects (as seen in patients with VIPoma) and beneficial haemodynamic effects.[112] To enhance the very short half-life of VIP, a peptide has been developed (Vasomera); it was found to be safe and well tolerated following a single injection in a study including patients with primary hypertension (ClinicalTrials.gov: NCT01523067, NCT01873885).

Future directions

The parenteral approach suggests that this drug could be used in the emergency setting.

Sodium transport as a target

Rationale

Intestinal sodium intake has been involved in the pathogenesis of hypertension and mainly related to the activity of electroneutral sodium/hydrogen exchangers located in enterocytes.[113]

Clinical trial data

Inhibition of sodium/hydrogen exchangers by orally administered tenapanor increases intestinal sodium excretion and lowers BP in an experimental model of HTN.[114,115] Similarly, an inhibitor of sodium-glucose co-transporter type 2, empagliflozin, has been investigated in a large outcome RCT and was associated with a reduction of the primary composite cardiovascular endpoint. In this case, increased urinary sodium and glucose excretion partly explained the decrease in BP in diabetic patients and suggests a promising new avenue in the field of sodium modulation for human hypertension.[116]

Future directions

Recent data suggest that this approach could be of interest for hypertensive diabetic patients and perhaps also be beneficial in patients with hypertension and heart failure.

Inhibition of noradrenaline synthesis

Rationale

Dopamine β-hydroxylase (DBH) is involved in the production of noradrenaline from dopamine in pre-ganglionic neurons.

Clinical trial data

Etamicastat is a reversible peripheral inhibitor of DBH which has been studied in mild-to-moderate hypertensive patients and led to a significant dose-dependent reduction in 24 ambulatory BP without any safety signal.[117]

Future directions

This new centrally acting drug could be used in difficult to control hypertensive patient or in hypertensives with dysautonomia.

Future tools and targets for drug development

Genetic and molecular aspect of hypertension:

Research in this field has moved on from studies of monogenic forms of hypertension to genome-wide association studies which have confirmed the role of common genetic variants in hypertension and are also helping to decipher novel pathways of BP regulation which could lead to drug optimization or new drug development.[118] A newly discovered pathway modulated by the uromodulin gene shows promise in yielding future drug targets.[119]

Evidence from genetic studies also suggests that mechanisms involved in the regulation of NPs could be considered as a potential target or marker of response. Hence, activators of NPs, such as corin, NP target receptors, or enzymes involved in the degradation of NP exhibit a level of expression or activity influenced by genetic variation.[120,121] Identification of these variants could explain response to drugs and potentially inform the future prognosis of patients and also identify new treatment targets for hypertension.

Immunity and inflammation

It has been recognized that immunity contributes to human hypertension.[122,123] Numerous stimuli involved in the pathogenesis of hypertension (e.g. angiotensin II, salt, and catecholamines) are also recognized to impact upon T lymphocytes (both number and type such as T regulatory/helper) and derived cytokines production (IL-17, IFN-γ, TNF-α, or IL-6) leading to both sustained BP elevation (through enhanced sodium retention, SNS activation, or increased vascular resistance) and end organ damage. Antihypertensive therapies are known to influence these factors such as MRA (spironolactone).[122] Moreover, hypertension, by increasing oxidative stress, also contributes to immune activation in hypertension through mechanisms involving dendritic cells.[123] However, in trials investigating drugs known to affect these pathways or cells (e.g. in the field of psoriasis), immunomodulation had no effect on BP. These observations potentially suggest a more active role of B lymphocytes and the need to further pursue our understanding of the interaction between immunity and BP. Abatacept, a fusion protein known to inhibit T-cell activation and used in various inflammatory condition, is currently being investigated as an adjunctive therapy in resistant hypertension (ClinicalTrials.gov: NCT02232880).

Dietary management of hypertension

A diet emphasizing flavonoid-rich fruits and vegetables achieves a BP reduction of approximately half that observed with the DASH diet.[124,125] The major pharmacodynamic effect was restoration of endothelial function, either directly, by affecting nitric oxide levels, or indirectly, through other pathways (i.e. antioxidant, anti-inflammatory, or acetylcholine -related). Quercetin has demonstrated the most consistent BP-lowering effect in animal and human studies, irrespective of dose, duration, or disease status.[126] However, further research on the safety and efficacy of the flavonoids is required before any of them can be used by humans, presumably in supplement form, at the doses required for therapeutic benefit.

Authors' contributions

M. L. handled funding and supervision. M.L., P.S., A.P. acquired the data. M.L., P.S., A.P. conceived and designed the research. M.L., P.S., A.P. drafted the manuscript. M.L., P.S., A.P. made critical revision of the manuscript for key intellectual content.

Conflict of interest: M.D.L. has received honoraria from Medtronic Inc., St Jude Medical, ROX Medical and Cardiosonic. P.A.S. is an employee of Rox Medical, Inc. He has stock options in Rox Medical, Inc., Cibiem Inc. A.P. has received speaker fees, consulting fees, or research grants or has been sponsored for medical meeting by: Ablative Solutions, Abbott, Astra Zeneca, BMS, CVRx, Daichii, Medtronic Inc., MSD, Novartis, Recor Medical, Servier, and St Jude Medical.

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