The role of sympatho-inhibition in combination treatment of obesity-related hypertension

Revathy Carnagarin¹, Cynthia Gregory¹, Omar Azzam¹, Graham S Hillis¹,², Carl Schultz¹,², Gerald F Watts¹,², Damon Bell¹,², Vance Matthews¹, and Markus P Schlaich¹,²,³

¹ Dobney Hypertension Centre, School of Medicine - Royal Perth Hospital Unit, University of Western Australia, Perth, and ²Department of Cardiology and ³Department of Nephrology, Royal Perth Hospital, Perth, Australia.

Word count: 2902 words (excluding references)

Correspondence to:
Professor Markus Schlaich
Dobney Chair in Clinical Research
School of Medicine - Royal Perth Hospital Unit
The University of Western Australia
Level 3, MRF Building, Rear 50 Murray St,
Perth WA 6000; Australia
Phone: +61 8 9224 0334 Fax: +61 8 9224 0374
email: markus.schlaich@uwa.edu.au
Abstract

Obesity related hypertension is commonly characterized by increased sympathetic nerve activity and is therefore acknowledged as a predominantly neurogenic form of hypertension. The sustained sympatho-excitation not only contributes to the rise in blood pressure but elicits a vicious cycle which facilitates further weight gain and progression of associated co-morbidities. While weight loss and exercise remain at the forefront of therapy for obesity and obesity related hypertension, the difficulties in achieving and maintaining long-term weight loss with life-style measures and the variable blood pressure response to weight loss often necessitate prescription of antihypertensive drug therapy. Remarkably there are no specific recommendations for pharmacologic treatment for obese patients with arterial hypertension in any of the current guidelines and general principles of antihypertensive treatment are applied. The use of β-blockers and diuretics is commonly discouraged as first or second line therapy due to their unfavourable metabolic effects. This review explores evolving therapeutic strategies which based on their interference with pathophysiologic mechanism relevant in the context of obesity may guide optimized treatment of obesity related hypertension.

Keywords: Obesity related hypertension; sympathetic activation; pharmacotherapy; antihypertensive medications; pathophysiology.
Introduction

The obesity pandemic is reaching a staggering expansion with a current prevalence of 40-60% and an expected increase to 75% of females and 83% of males by 2025 in industrialized countries such as Australia and the US. Obesity along with its associated co-morbidities and mortality has emerged as a worldwide threat to population health and enormous economic burden in many countries [1]. According to the World Health Organization, ‘Obesity is one of the most important contributors to ill health’. There is concern that any gains made in reducing cardiovascular disease may actually be reversed by the obesity epidemic [2]. Given the large increase in the number of overweight and obese individuals, the proportion of hypertensive patients who are obese is likely to increase sharply in the future. Thus, many patients with arterial hypertension are exposed to the additional metabolic and cardiovascular risk associated with obesity.

Obesity is more than a co-morbid condition because it can cause or worsen arterial hypertension in susceptible individuals. Large-scale epidemiological studies such as NHANES and Framingham suggest a tight correlation between body weight and blood pressure. Statistical analysis of this data suggested that 60–70% of hypertension may be directly attributable to excess adiposity, both in men and in women [3]. The age-adjusted relative risk for the development of hypertension was 1.75 in men and 1.46 in women [4]. Regression models based on random population samples, corrected for the age-related rise in blood pressure (BP) demonstrated a stable linear relationship of adiposity with BP across developed and developing countries. In this cross sectional health examination survey involving 3116 adults not treated for hypertension (age range: 35-64), the systolic BP increased by 1mmHg for a gain of 1.7kg/m2 and 4.5cm (men), or 1.3kg/m2 and 2.5cm (women) in body mass index or waist circumference, respectively [5]. Another 11 year prospective population study confirmed a strong positive causal association between changes in BMI and changes in BP [6].

Clinical trials indicated that loss of original body weight (around 10%) resulted in clinically significant reductions in blood pressure and cardiovascular mortality [7, 8]. Contemporaneous studies indicated that increased adiposity resulted in metabolic abnormalities which in concert with hypertension, resulted in the development of cardiorenal and metabolic syndrome [9,10], features that are mediated to a large extent by sustained activation of the sympathetic nervous system [11]. Further support for a dominant role of the sympathetic nervous system in this context stems from studies demonstrating sympatho-inhibitory effects of diet and/or exercise-induced weight loss on BP and relevant metabolic
markers [12]. Thus the concept of sympathetic overdrive has emerged as a major cause of obesity-induced morbidity and cardiovascular mortality and functions in a feedforward manner to sustain obesity itself.

While lifestyle modification is clearly effective in reducing excess body weight and improving various aspects of the cardiovascular (CV) and metabolic consequences of obesity, the majority of patients fail to implement and sustain appropriate lifestyle changes. Anti-hypertensive combination therapy is very frequently required in obesity-related hypertension (OH) for CV risk reduction and BP lowering. While current hypertension guidelines do not provide specific recommendations for treatment of OH, inhibitors of the renin-angiotensin system such as ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs) are widely considered as first choice due to their favourable side effect profile, documented cardiorenal protection and additional beneficial metabolic effects. Most hypertension guidelines generally recommend calcium channel blockers (CCBs) and diuretics as the appropriate add-on drugs if combination therapy is required. In the context of OH, CCBs appear as a preferred combination due to their powerful BP lowering capacity, particularly in combination with RAS blockers and their neutral effect on metabolic parameters, whereas diuretics seem less favourable in view of their unwanted metabolic side effects including worsening of insulin resistance and exacerbation of gout. Given the important role of sympathetic activation in obesity the use of β-blockers may seem as plausible antihypertensive option, however their association with weight gain and other adverse metabolic consequences such as worsening of insulin resistance makes them less than ideal in OH. Robust evidence for a potentially preferable antihypertensive combination therapy for OH has yet to be established. Here we review important aspects including the pathophysiology underlying OH, available evidence for existing management strategies and other relevant findings that may guide the identification of a preferred combination treatment tailored to the specific features and complications of OH.

**Pathophysiology of Obesity Hypertension**

OH is a complex disorder resulting from the interplay of multiple factors perturbing normal cardiometabolic homeostasis (Figure 1). In lean hypertensive individuals, much of the hypertension is driven by an increase in systemic vascular resistance. By contrast, in obese hypertensive individuals, the hypertension is at least partly explained by increased cardiac
output [13]. The increase in cardiac output may result from sympathetic activation and plasma volume expansion due to sodium retention [14]. Obese hypertensive patients clearly exhibit an increase in sympathetic activity as assessed by noradrenaline spillover, particularly sympathetic outflow to the renal vascular bed further promoting volume retention, alterations in renal blood flow, and release of renin from the juxtaglomerular apparatus, thereby engaging the renin-angiotensin-aldosterone cascade [15]. Baroreflex dysfunction and the sleep apnea syndrome, a common co-morbidity in obese subjects, may also contribute to sympathetic overactivity [16, 17]. Pharmacological studies and direct recordings of sympathetic nerve activity suggest that the sympathetic nervous system contributes substantially to obesity-associated arterial hypertension [18, 19] and is characterized by distinct differences in the firing pattern of sympathetic neurons in human obesity [20].

Sympathetic tone is also exaggerated by the obesity induced derangement in pressure natriuresis. As stated by Guyton’s hypothesis, sustained hypertension is the result of abnormal relationship between arterial pressure and natriuresis. Whereas increased pressure results in enhanced sodium excretion to reduce hypertension in the normal scenario [21], the obesity-related alterations such as the enhanced sympathetic tone, activation of the renin-angiotensin-aldosterone system (RAAS), hyperinsulinemia, and renal structural changes significantly impair the pressure-natriuresis curve. Sympathetic blockade (combined α- and β-blockade) prevents OH in experimental animals and in patients [18, 22-25]. Renal denervation altered the pressure-natriuresis relationship in OH animal models [22-29]. Similarly, leptin secreted by adipocytes to produce satiety and weight loss increases sympathetic overdrive to induce thermogenesis, at least in experimental studies. Also, hyperleptinemia stimulates the hypothalamic pro-opiomelanocortin (an important weight modulator) pathway and further exaggerates central sympathetic outflow. Mutations in the melanocortin 4 receptor produce hypertension in man, thereby demonstrating the regulatory capacity of the melanocortin pathway in blood pressure and weight regulation [24, 30].

Exaggerated RAAS activation with high circulating renin, angiotensinogen, and angiotensin II, despite augmented renal sodium retention is seen in OH [23-24, 27, 29, 31]. Adipose tissue endogenously synthesizes and increases the circulating angiotensinogen in obesity which enhances the production of angiotensin I and angiotensin II [31]. Angiotensin II further increases renal tubular sodium reabsorption and stimulates synthesis of aldosterone, thereby promoting sodium and fluid retention. Similarly, obesity associated
hyperinsulinemia [27, 28] elevates arterial pressure as insulin enhances tubular sodium reabsorption. The effect of angiotensin-converting enzyme inhibitors and peroxisome proliferator-activated receptor gamma agonists on blood pressure supports the role of the RAAS and hyperinsulinemia in this context [32-34]. The endocannabinoid system, though less well-understood may have a role in OH. Obesity is associated with increased levels of endocannabinoids in several tissues and in the circulation. The cannabinoid receptor 1 inverse agonists, rimonabant and tariabant produced weight loss and ameliorated obesity-related metabolic impairments [32-34].

**Strategies for the management of Obesity Hypertension**

Obesity and arterial hypertension frequently coexist. Obesity can cause or worsen arterial hypertension and is a common cause of resistance to antihypertensive treatment. Moreover, the associated risk profile differs markedly between lean and obese patients with arterial hypertension. Current guidelines do not provide specific recommendations for pharmacologic treatment of obese patients with arterial hypertension. This state of affairs exists due to the lack of data from clinical trials, an incomplete understanding of the underlying pathophysiology, and perhaps neglect by the scientific and clinical community. The various management strategies for OHT are summarised in Figure 2.

**Lifestyle modification**

Weight loss and exercise remain at the forefront of therapy for obesity and OH. Short term exercise training has consistently been shown to be associated with a reduction in sympathetic activity and an improvement in blood pressure. We have shown that in subjects with the metabolic syndrome, weight loss following a 12 week dietary program was accompanied by a significant reduction in sympathetic nervous activity and an improvement in all components of the metabolic syndrome [13, 35]. In clinical practice however, the majority of patients fail to implement and sustain appropriate lifestyle changes in the long term.

**Pharmacologic antihypertensive treatment**

Given the difficulties in achieving and maintaining long-term weight loss with life-style measures and the variable blood pressure response to weight loss, many obese hypertensive patients ultimately require antihypertensive combination drug therapy, with 2 or 3 antihypertensive drugs to achieve BP control [36]. Remarkably, current hypertension
guidelines do not provide specific recommendations for the choice of antihypertensive medications. Indeed, there are no larger trials addressing this issue [37]. Therapeutic decisions have to be made on the basis of few existing data, including our current understanding of the mechanisms involved in OH and the presence or absence of target organ damage or cardiovascular disease in individual patients. Furthermore, attention to potential beneficial effects beyond blood pressure lowering or adverse and unwanted metabolic effects of certain drug classes may favour or limit their respective use. For example, β-blockers reduce cardiac output and renin activity, both of which have been shown to be increased in obese patients. It is therefore not surprising that β-blockers alone [38], or in combination with α-adrenoreceptor blockers [39], were more effective in decreasing blood pressure in obese than in lean hypertensive individuals. However, substantial limitations for the use of β-blockers, especially in young obese hypertensive patients without cardiac and renal complications, are related to their well described unfavourable effects on glucose metabolism and increase in body weight [40, 41]. Whether newer vasodilating β-blockers may be better alternatives remains to be determined. Similarly, while diuretics are useful in counteracting the volume overload frequently evident in obesity hypertension, their adverse metabolic effects and their capacity to further exaggerate the already increased sympathetic drive renders them a suboptimal choice.

In view of their broad spectrum of beneficial effects, excellent tolerability, proven cardiovascular protection and beneficial effects on metabolic aspects, inhibitors of the RAAS, in particular ACE-inhibitors and ARBs are widely considered to be the most appropriate first line drug for antihypertensive treatment of obese patients [42].

CCBs are effective antihypertensive drugs and considered neutral in regards to their metabolic effect. However, some data suggest that CCBs may be less effective in severely obese subjects, possibly through their accompanying sympathoexcitation. Furthermore, fluid retention and peripheral oedema can limit their utility [43].

Given the unequivocal evidence for an important role of increased sympathetic outflow in many of the features characteristic of OH, it is perhaps surprising that centrally acting sympatholytic agents such as Imidazoline I1 agonists, which effectively inhibit sympathetic outflow at the level of the rostral ventrolateral medulla (Figure 1), are not frequently
considered in the treatment of OH. Aside from their blood pressure lowering capacity which is comparable to that of other drug classes, agents such as moxonidine have been demonstrated to improve glucose metabolism, insulin sensitivity and dyslipidemia [44, 45]. Furthermore, their use has been associated with a reduction in the progression of microalbuminuria and renal dysfunction, common features observed in obese subjects [46, 47]. Other beneficial effects on end organ function include a reduction in left ventricular hypertrophy [48] and improvement in endothelial function [49].

Most recently, another potentially highly relevant link in the current context has been described between sympathetic activation and expression of the sodium glucose co-transporter-2 (SGLT-2) [50]. SGLT-2 is relevant for renal sodium handling and inhibitors of SGLT-2 have shown to improve glucose control but perhaps more importantly to reduce CV events in patients with diabetes [51]. In this study by Matthews et al. noradrenaline, the main neurotransmitter of the sympathetic nervous system was shown to upregulate SGLT-2 expression in human proximal tubular cells. [50]. Inhibition of central sympathetic outflow with the resulting reduction in circulating noradrenaline could be an important mediator of sympathoinhibition-induced improvement of glucose metabolism via SGLT-2 regulation, thereby potentially further favouring such an approach in obesity hypertension.

A recently published large observational study in 5603 patients with overweight/obesity related BP elevation and metabolic disturbances (MERSY study) investigating the effects of moxonidine alone or in combination with other BP lowering medications demonstrated favourable effects not only on BP but a number of relevant metabolic markers in a primary care setting [52]. While clearly limited by the observational nature and the lack of a control group, the findings from this study provide evidence for a substantial BP lowering effect and clinically relevant improvements in metabolic markers such as body weight, fasting glucose levels and lipid profile.

In addition, a small, randomized, open parallel study in obese hypertensive subjects compared the effects of moxonidine (0.2mg-0.4mg/d; n=19, BMI=35.4±1.7kg/m2) and amlodipine (5-10mg/d; n=21; BMI=35.9±1.4kg/m2) as stand-alone therapy [53]. The reduction in ambulatory systolic BP was substantial in both groups (moxonidine: from 144.1±4.2 to 133.8±3.1mmHg vs amlodipine: from 145.4±4.4 to 129.0±1.9mmHg) without a statistically significant difference in the change in BP between the two groups. However, up-
titration of medication was to the highest recommended dose of amlodipine (10mg/d) but only to a moderate dose of moxonidine (0.4mg/d, highest recommended dose is 0.6mg/d) [54]. Nevertheless, moxonidine administration reduced the supine arterial plasma levels of adrenaline from 63.2±6.6 to 49.0±6.7 pg/ml (p<0.005), the supine arterial plasma levels of noradrenaline from 187.9±10.7 to 149.7±13.2 pg/ml (p<0.01) and the orthostatic venous plasma levels of noradrenaline from 258.6±25.0 to 190.3±16.4 pg/ml (p=0.03). None of those variables were changed by amlodipine. The plasma levels of leptin and insulin 120 min after a glucose load decreased after moxonidine administration from 27.2±3.5 to 22.6±2.9 pg/ml (p<0.05) and from 139.7±31.2 to 76.0±15.2 U/ml (p<0.05), respectively. Amlodipine, however, did not modify those variables. While limited by its small sample size, this study provides important preliminary data to support the pathophysiologically sound notion that in obesity hypertension a therapeutic approach targeting central sympathetic outflow may not only provide substantial and effective BP lowering but beneficially impact on a number of relevant metabolic markers relevant for cardiovascular risk. A larger scale active comparator study, ideally on background medication with RAS blockade to properly compare the BP and metabolic benefits of a CCB vs Imidazoline I agonist would be highly relevant to inform on the most adequate antihypertensive approach for obesity hypertension when combination therapy is warranted.

Conclusions and future directions
Antihypertensive combination treatment is required in the vast majority of hypertensive patients, particularly in obese hypertensives. Inhibitors of the renin angiotensin system are considered first line choice due to additional beneficial effects on metabolic control. Most hypertension guidelines generally recommend CCBs and diuretics as preferred combination partners. However, in obesity related hypertension diuretics have unwanted metabolic side effects, leaving CCBs as a preferred second line choice. We and others have provided substantial evidence to indicate that sympathetic overactivity is a cardinal feature of obesity related hypertension that not only impacts on BP but also metabolic control. Targeting sympathetic overactivity therapeutically may therefore be of specific use in OH and combining RAS blockade with a centrally acting sympatholytic agent compared to a CCB (amlodipine) may provide better blood pressure and metabolic control and have positive implications for cardiovascular risk reduction. Sympathoinhibition may therefore emerge as a preferred second line treatment choice for obesity related hypertension, a proposition that requires thorough clinical testing.
Sources of Funding
None

Disclosures
MPS is supported by an NHMRC Research Fellowship and has received consulting fees, and/or research support from Abbott. None of the other authors declare any conflict of interest relevant to this manuscript.
References

Papers of particular interest, published recently, have been highlighted as: • Of importance


50. • Matthews VB et al. Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2. J Hypertens. 2017, 35: 2059-2068. This is the first study to identify the importance of SNS-SGLT2 cross talk that accounts for SNS-induced alterations in glucose metabolism and SGLT2 inhibition with dapagliflozin resulted in cardiovascular and renal protection.

51. • Zinman B et al. EMPA-REG OUTCOME Investigators. 27 Version 2, dated 25 June 2016 Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 ; 373: 2117-2128. A randomized control trial where type 2 diabetics at high risk for cardiovascular events received empagliflozin along with standard care had a lower rate of the primary composite cardiovascular outcome and death as compared with placebo.


Figure 1: Pathophysiologic aspects of obesity-related hypertension
Figure 2: The various management strategies for obesity-related hypertension