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Resistant Hypertension and Chronic Kidney Disease: a Dangerous Liaison

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Abstract Treatment-resistant hypertension is an increasingly recognised problem and is markedly over-represented in patients with chronic kidney disease (CKD). Recent evidence has clarified the heightened risk for both adverse renal and cardiovascular outcomes associated with resistant hypertension, even when blood pressure control is attained. The diagnosis of resistant hypertension in CKD is reliant on accurate blood pressure measurement, and out of office measurements are important due to the high prevalence of masked hypertension in these patients. Treatment strategies include careful dietary measures to restrict sodium intake, and a focus on improving adherence to antihypertensive medications. Medication choices should focus on a sensible foundation and then diuretic titration to combat the salt and volume retention inherent in CKD. In this review, we discuss the epidemiology, pathogenesis and consequences of resistant hypertension in CKD, and then review the optimal diagnostic and management strategies.

Keywords Resistant hypertension · Chronic kidney disease · CKD

This article is part of the Topical Collection on *Resistant Hypertension*

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Introduction

Hypertension is a common clinical problem and considered one of the most significant risk factors for mortality on a global scale [1]. A proportion of hypertensive patients can be said to be treatment resistant, failing to achieve target blood pressures despite appropriate drug therapy and this appears to carry with it an increased risk of complications. Chronic kidney disease (CKD) is another common and growing problem and interacts on many levels with hypertension and particularly resistant hypertension. As the kidneys are an important determinant of blood pressure via multiple important pathways, it is not perhaps surprising that this relationship exists, but it also has important implications for diagnosis and treatment. In this review, we will discuss epidemiological and diagnostic issues pertinent to resistant hypertension and CKD, as well as aspects of pathogenesis, complications and management strategies in this patient group.

Definitions

Resistant hypertension has been defined by consensus as a blood pressure above target despite the use of three appropriately dosed antihypertensive agents including a diuretic [2]. The group of patients who attain blood pressure control but require a large number of medications to do so has also been defined, often called 'controlled resistant' hypertension, with blood pressure controlled to target with four or more drugs [2]. The appropriate target blood pressure has however been the subject of some debate, with a recent shift to higher targets. The Kidney Disease Improving Global Outcomes (KDIGO) blood pressure guidelines (2012) suggest a target of <140/90 mmHg in non-proteinuric renal disease and a tighter target of <130/80 mmHg in those with significant proteinuria [3],

targets largely endorsed by other international groups [4, 5]. Some recent guidelines have however set higher targets of <140/80 mmHg for all CKD patients, citing insufficient evidence for lower targets even in those with proteinuria [6, 7]. The recently reported SPRINT trial however demonstrated a reduction in all-cause mortality and cardiovascular outcomes with a lower systolic target of 120 mmHg compared to 140 mmHg in a large cohort of patients at an increased cardiovascular risk, including 2648 participants with mild–moderate CKD [8•]. Notably, patients with diabetes and more severe renal disease or proteinuria >1 g/day were excluded. The optimal target is therefore not entirely clear, and the definition of resistant hypertension in CKD thus should be determined carefully when evaluating and comparing studies involving this patient cohort.

Epidemiology

In the general hypertensive population, the prevalence of resistant hypertension varies amongst reports. Persell et al. examined data from one of the National Health and Nutrition Examination Survey (NHANES) cohorts (2003–2008) using office blood pressures and reported that 12.8 % of drug-treated hypertensive patients met the criteria for resistant hypertension [9]. In a sample from an Eastern European cross-sectional study, 19.4 % of patients were reported to have 'true'-resistant hypertension (pseudo-resistant hypertension due to white coat effect excluded by out of office measurements and a limited assessment of adherence performed by an individual physician judgement) [10]. Other studies have reported lower estimates, such as the study by Daugherty et al., who used insurance registry data [11] to establish a large cohort with incident hypertension, finding that 1.9 % of these patients developed resistant hypertension during a median follow-up period of 1.5 years. In such studies, CKD is universally more common amongst patients with resistant compared to non-resistant hypertension, though the prevalence of resistant hypertension in a less-selected CKD cohort is less clear. In one study of consecutive hypertensive, patients referred to a specialist CKD clinic [12], after the exclusion of pseudo-resistance, the prevalence of resistant hypertension was 26 % at referral, increasing to 38 % after 6 months (the increase largely due to upward drug titration). Another study from a large and less-selected-population-based cohort found that the prevalence of apparent resistant hypertension increased when participants were stratified by eGFR, from 15.8 % in those with an eGFR>=60 ml/min to 24.9 % in those with an eGFR of 45–59 ml/min and 33.4 % amongst those with an eGFR of <45 ml/min [13]. A similar stratification of prevalence was found when patients were sub-divided according to the albumin/creatinine ratio, with a remarkably high prevalence of resistant hypertension of 48.3 % found in those with an albumin/creatinine ratio of >300 mg/g. Notably, this study used home blood pressure measurements and defined resistant hypertension as >140/90 mmHg, a generous definition given that home blood pressures tend to be lower than office and closer to ambulatory than office readings.

Resistant hypertension is therefore very common amongst patients with CKD, with the prevalence appearing to be proportional to the degree of renal dysfunction and in excess of that seen in patients with normal renal function.

Diagnostic Issues

The diagnosis of resistant hypertension requires the exclusion of 'pseudo-resistant hypertension', that is, hypertension which is treatment resistant due to another factor (Table 1). These factors can vary from poor medication adherence to improper blood pressure measurement and white coat effect. Evidence suggests that the prevalence of true-resistant hypertension may be lower than historically estimated once these explanations have been excluded, particularly those related to suboptimal medication adherence [14, 15]. Less information is available in the setting of CKD, but efforts should be made to exclude poor medication adherence before the label of resistant hypertension is applied. Such methods might include verifying drug dispensing, trialling directly observed therapy or even measuring drug metabolites.

In general, office blood pressure measurement overestimates ambulatory blood pressure, and obtaining out of office measurements will reclassify a significant proportion of patients. The prevalence of white coat hypertension is significant in CKD. In a study in which 550 CKD patients with hypertension were screened, 128 (23 %) were excluded because of white coat hypertension (91 by home blood pressures and 29 by ambulatory blood pressure measurement (ABPM)) [12]. In a meta-analysis of six studies and 980 patients, the overall prevalence of white coat hypertension in CKD was 18.3 % [16]. Importantly, amongst CKD patients with office hypertension, those with controlled ambulatory systolic blood pressures have a much lower cumulative risk of progressing to end stage renal failure (ESRF), highlighting the importance of excluding white coat effect [17].

Just as importantly, out of office measurements can reclassify patients with normal office blood pressures but ambulatory hypertension, often called 'masked hypertension'. The prevalence of masked hypertension in CKD appears to be remarkably high in some studies. In a cross-sectional study of 1075 Japanese CKD patients studied with ABPM and office measurements, the prevalence of masked hypertension was 30.9 %, and 56.9 % of patients were hypertensive based on ambulatory readings compared to 31.6 % on office readings [18]. In a recent prospective study of 333 CKD patients, the prevalence of masked hypertension by ambulatory

Table 1 Example potential causes for 'pseudo-resistant hypertension'

Causative factor	Prevalence	Solution
White coat effect	In CKD ~18–25 % [12, 16]	Ambulatory blood pressure measurement, home blood pressure measurement, automated office measurement
Improper BP measurement	Unclear	Education, clinic protocols, nurse specialists
Medication non-adherence	In CKD unclear, in other resistant hypertension populations up to 50 % [15]	Directly observed therapy, dispensing records, drug level screening, dosettes, etc., home BPs, education, regular frequent review
Suboptimal antihypertensive regiment	Unclear	Rationalise medication, titrate or intensify diuretics
High-salt intake	In CKD unclear but likely common	Education, dietician guidance

average was 32.8 %, and 50.8 % by home blood pressure measurement, though the home readings were poorly reproducible when repeated after a month [19]. CKD patients with masked hypertension appear to have a higher cumulative risk of ESRF compared to those with controlled ambulatory pressures and a higher burden of end organ damage compared to normotensive CKD patients [20, 21].

Out of office blood pressure readings are therefore an important tool which should be used in all patients suspected of having resistant hypertension to help exclude pseudo-resistance and arguably in most patients with CKD to avoid missing masked hypertension, which could be resistant. If out of office measurements are unavailable or impractical, then automated office readings may be a reasonable substitute [22].

Consequences

The high prevalence of resistant hypertension in CKD reflects the importance of the kidneys to blood pressure control and the bidirectional relationship between these diseases—CKD exacerbates hypertension and causes treatment resistance and hypertension of increasing severity accelerates the progression of CKD.

There is a large body of observational evidence linking severity of hypertension with progression to ESRF. In a cohort of more than 300,000 men screened for the MRFIT study in the 1970s, a linear and independent relationship was seen between systolic and diastolic blood pressures and the incidence of ESRF over an average of 16 years of follow-up [23]. In a more recent large retrospective cohort study of more than 470,000 hypertensive patients followed over 5 years, the adjusted hazard ratio for ESRF between resistant hypertension (either controlled or uncontrolled) vs. non-resistant hypertension was 1.32 (95 % CI 1.27–1.37) [24•]. Because of the large number of patients in this study, the investigators were able to formulate comparisons between controlled resistant, uncontrolled resistant and non-resistant hypertension. They demonstrated that the highest hazard ratio for ESRF was between uncontrolled resistant and non-resistant hypertension (HR 1.45, 95 % CI 1.39–1.52). Interestingly, amongst patients with resistant hypertension, those with uncontrolled resistant hypertension had a higher hazard ratio for ESRF than those with controlled resistant hypertension (1.25, 95 % CI 1.18–1.33), and patients with controlled resistant hypertension had an increased HR for ESRF when compared to those with non-resistant hypertension (HR 1.16, 95 % CI 1.10–1.22). This suggests that attaining blood pressure control ameliorates most, but not all of the increased risk of renal target organ damage associated with treatment-resistant hypertension.

Beyond the association with worse renal outcomes, resistant hypertension is associated with a higher incidence of adverse cardiovascular outcomes. This is of course important because more patients with CKD die of cardiovascular causes than develop ESRF [25]. The hazard ratio for cardiovascular events was 1.47 (95 % CI 1.33–1.62) for patients with resistant hypertension vs. well-controlled hypertension in one large study [11] and 1.24 (95 % CI 1.2–1.28) for ischaemic heart events and 1.46 (95 % CI 1.4–1.52) for congestive heart failure in a similar comparison in the large study reported by Sim et al. [24•].

Pathogenesis

There are several potential mechanisms by which CKD could exacerbate hypertension and contribute to treatment resistance, and chief amongst these is the importance of the kidneys to sodium balance. A reduced number of functioning nephrons and lowered glomerular filtration rate result in a reduced ability to excrete a high-sodium load, leading to volume expansion and hypertension. Indeed, patients with resistant hypertension appear to be particularly salt sensitive—in one small cross-over interventional trial of 12 subjects with resistant hypertension, the difference in office blood pressures during a high (250 mmol/day) and low (50 mmol/day) diets was 22.7/9.1 mmHg [26]. These patients had a relatively

normal renal function, but a recent randomised study of 20 CKD patients with resistant hypertension (baseline 24 h BP 151/82 mmHg) found the difference between a 60–80 mmol/day and a 200 mmol/day diet to be 10/4 mmHg (ambulatory pressures) [27•]. This study also demonstrated a significant reduction in proteinuria with the low-salt diet. Sodium reduction enhances the anti-proteinuric effects of angiotensin II receptor blockade and works synergistically with diuretics to reduce proteinuria [28]. This suggests that excess sodium intake in CKD contributes to glomerular dysfunction (possibly by promoting glomerular hyperfiltration) in ways which are only partially addressed by inhibition of the renin angiotensin system and diuretics [28, 29].

CKD also contributes to accelerated vascular ageing and atherosclerosis, factors which both promote increased arterial stiffness and systolic hypertension [30, 31]. Patients with resistant hypertension are also more likely to be older and have diabetes [10–12], factors which contribute both to the development of CKD and also to increased arterial stiffness. CKD is also associated with an increased sympathetic activity, which aggravates hypertension and is associated with a resistant hypertensive phenotype [32].

Secondary causes of hypertension are relatively common in resistant hypertension, and guidelines suggest that all patients with resistant hypertension should be screened for their presence [33]. In particular, the prevalence of primary aldosteronism in resistant hypertension has been reported to be as high as 20 % in some series [34]. Primary aldosteronism promotes glomerular hyperfiltration and is associated with albuminuria and CKD [35–37].

Screening for primary aldosteronism usually utilises the aldosterone/renin ratio, but this may be confounded in CKD, in which declining numbers of juxtaglomerular cells and the tendency to sodium retention can result in lower renin levels, whilst hyperkalaemia tends to stimulate aldosterone, and hence a false-positive aldosterone/renin ratio may result [38]. Additionally, many drugs which are commonly used for the treatment of hypertension in CKD can profoundly alter aldosterone and renin levels and make diagnosis difficult unless they are temporarily withdrawn, which can be challenging or even frankly impractical in the setting of resistant hypertension [38]. Removal of an aldosterone-producing adenoma can result in a fall in eGFR and apparent worsening of CKD, likely as a result of the correction of hyperfiltration [35, 39]. Fortunately, this appears to stabilise in the longer term after treatment [37]. Although a firm evidence base is lacking, it would seem sensible to screen for primary aldosteronism in resistant hypertension in milder grades of renal dysfunction (CKD 1–3), but perhaps to be more cautious in a more advanced disease where the chances of false positives are possibly higher and the consequences of treatment less clear.

Obstructive sleep apnoea (OSA) is an extraordinarily common condition in the setting of resistant hypertension, with an apparent prevalence of >70 % [40–42]. The exact mechanism of this relationship is not entirely clear, but it appears to be linked with primary aldosteronism and salt and volume retention, which could increase upper airway resistance and exacerbate sleep apnoea [43–46]. A similarly high prevalence of OSA is seen in CKD patients, and evidence suggests that this may also be related to a volume overload and rostral fluid shifts [47–49]. Treatment of OSA with CPAP appears to modestly reduce blood pressure in hypertensive patients [50, 51], but treatment with diuretics (especially mineralocorticoid antagonists) also appears to reduce blood pressure and the severity of sleep apnoea, supporting a link to salt and volume retention [52, 53].

Atherosclerotic renal artery stenosis is another secondary cause of hypertension which is also associated with CKD [54]. Randomised trial evidence does not suggest a therapeutic effect of intervention in most cases in regards to renal or blood pressure outcomes [55–57]. These trials have however selected patients for intervention largely on the basis of radiological criteria for renal artery stenosis rather than functional evidence of renin-driven hypertension. Observational evidence suggests that carefully demonstrated dominance of renin secretion from a kidney with an apparent stenotic artery may predict good blood pressure outcomes from intervention, including patients with CKD and resistant hypertension [58]. A reasonable approach would be to screen for renal artery stenosis in patients with mild CKD and other features suggestive of renovascular hypertension, such as deteriorating renal function with renin angiotensin system blocking drugs, peripheral vascular disease or the presence of a renal bruit.

Treatment Strategies

Lifestyle Measures Including Dietary Salt Restriction

Excess salt intake is common amongst patients with resistant hypertension and is one of the most important avenues for improving blood pressure control in this patient group. Intervention studies demonstrate that the blood pressure-reducing effects of salt restriction in patients with resistant hypertension and CKD are at least as great as those seen in milder forms of hypertension [26, 27•, 59]. Dietary sodium restriction is also likely to magnify the effects of antihypertensive drug therapy, particularly diuretics and agents targeting the renin angiotensin system. Dietician input should therefore be part of the management of all patients with resistant hypertension and CKD, targeting a sodium intake of <2 g/day (90 mmol, equivalent to 5 g of sodium chloride) [3]. Obstructive sleep apnoea should be diagnosed where present and treated with CPAP [50, 51]. Regular exercise should also be recommended to patients, as this has beneficial effects on

blood pressure in CKD as well as wider benefits to cardiovascular fitness and quality of life [60].

General Drug Strategies

In the treatment of resistant hypertension adherence to therapy is arguably the most important factor to consider. Drug non-adherence is a common problem with complex causes and is associated with poor outcomes [61, 62]. An important strategy to improve adherence is to use once daily dosing where feasible with simplified, fixed dose combination therapy to decrease pill burden and tolerability [63]. The availability of combinations including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), a calcium channel blocker and a thiazide-like diuretic have made this approach practical, and most patients with CKD and resistant hypertension should be on one of these drugs as a cornerstone of treatment [64]. An algorithm for titration beyond this might include the trial of a mineralocorticoid antagonist and/or intensification of diuretic therapy, with the subsequent trial of a 'fourth line' drug if blood pressure is still not at target. The merits of individual drug classes are discussed further below.

Other interventional techniques to improve adherence include educational approaches to improve health and medication literacy, but effects have been mixed [65, 66]. Continued drug titration when blood pressure targets are not met is also clearly important for treating resistant hypertension, but clinical inertia is a surprisingly common issue in hypertension management [67–69]. Home blood pressure monitoring may be a useful strategy for some patients to improve adherence by enhancing patient involvement and could also aid drug titration.

ACE Inhibitors/ARBs

All hypertensive CKD patients should be treated with an ACE inhibitor or ARB if tolerated, based on their well-proven efficacy and relatively low side effect profile, and on the improvements in hard outcomes in CKD with proteinuria [70, 71]. In patients without proteinuria, the superiority of these drugs over other classes is not proven. Dual use of an ACE inhibitor and ARB has not been generally recommended, due to a lack of evidence for superiority and evidence for harm both in those with and without significant renal dysfunction in randomised trial settings [72, 73]. Interestingly, however, a recent large network meta-analysis of trials suggested that dual therapy might be more efficacious than either class of drug alone for the outcome of preventing progression to ESRF in diabetic kidney disease at the expense of a higher risk of acute kidney injury and hyperkalaemia [74•]. As such there may still be some place for limited use of this approach in selected patients.

In most patients, the modest reduction in eGFR (up to 30 % increase in creatinine) seen with the introduction of an ACE inhibitor or ARB is not an indication for drug cessation [3], but occasionally, patients will be unable to tolerate these drugs due to progressive renal dysfunction. Care must also be taken when introducing these drugs in patients with CKD 4–5, where the risk of hyperkalaemia and acute kidney injury is higher, but beneficial protective effects are still present [75].

Diuretics

In resistant hypertension, the drug regimen should include a diuretic, given the importance of sodium in the pathogenesis of hypertension in CKD. In milder CKD, long-acting thiazides and thiazide-like diuretics such as chlorthalidone should be favoured. In the non-CKD population, chlorthalidone is possibly superior to hydrochlorothiazide and is certainly more potent at an equivalent dose [76, 77]. In more advanced CKD, the effects of thiazides have been thought to be limited; however, recent evidence challenges this notion. In a study of 60 hypertensive CKD patients, 25 mg of chlorthalidone added to a non-diuretic regimen induced a reduction of ~19 mmHg systolic, with this drop also seen in the subset of 9 patients with an eGFR of 15–29 ml/min [78]. If there is suboptimal response to thiazides despite dose titration or if there is significant oedema or evidence of marked fluid overload, loop diuretics should be used, especially at lower eGFRs. Short-acting loop diuretics should be dose twice daily, and larger doses are typically needed in the advanced CKD, where the proportion of loop diuretic secreted into the tubule can decrease dramatically [79].

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor (MR) antagonists such as spironolactone or eplerenone have been shown to be the most effective add-on agents for resistant hypertension, with a number of small studies summarised in two recent meta-analyses [80, 81]. The estimates for an average reduction in blood pressure have varied from 16.5/4 to 24.3/7.8 mmHg depending on the method of analysis. A recent randomised crossover trial further confirmed the superiority of spironolactone over bisoprolol or doxazosin as an add-on therapy in a group of 285 patients with resistant hypertension [82]. In patients with CKD however, caution is needed with this class of drug due to the risk of hyperkalaemia. In a Cochrane review, MR antagonists added to ACE or ARB therapy increased the risk of hyperkalaemia twofold (95 % CI 1.25–3.0) in patients with mild to moderate CKD [83]. These risks are dependent on the baseline GFR and potassium, the dose of the drug and concomitant medications. In general patients with mild CKD (GFR >30 ml/min/1.73 m^2) and a low-normal baseline potassium (<4.5 mmol/L) can be safely trialled on low-dose

spironolactone (12.5–25 mg/day) with careful monitoring of potassium and eGFR.

Other Agents

Calcium channel blockers are useful antihypertensives which can be used safely in patients with CKD, and their easy availability in combination tablets with other drugs is very useful to simplify therapy. Non-dihydropyridines (diltiazem and verapamil) may reduce proteinuria compared to dihydropyridines, and thus may be preferred in patients without significant left ventricular dysfunction or conduction delay [84]. Further agents which could be considered 'fourth-line' include beta-blockers, which are especially useful where comorbidities such as ischaemic heart disease or heart failure are co-indications. Beyond this alpha blockade, direct vasodilators and centrally acting drugs can be trialled, but all are essentially empirical treatments and a cautious approach is needed due to the greater chance of side-effects.

Future Directions

Combination Diuretic Therapy

Given the importance of sodium retention to resistant hypertension, intensification of diuretic therapy targeting multiple nephron segments has been postulated as a potential treatment option. This has been demonstrated as a highly effective technique in a study of patients with resistant hypertension but normal renal function [85], and there has also been an interest in combining diuretics to avoid adverse effects of a high dose of a single drug class [86]. Combination diuretic therapy with loop and thiazide diuretics is typically used in CKD where there is significant volume overload and diuretic resistance but not specifically for hypertension control, though there has been some recent limited evidence suggesting this may be effective [87, 88]. Further exploration of diuretic combinations for resistant hypertension in CKD is warranted, though careful monitoring of renal function and electrolytes would be important.

Treatment of Hyperkalaemia Induced by RAS Blockade

Hyperkalaemia is a common problem in CKD, and this is exacerbated by the use of renin angiotensin system inhibitors and especially the use of MR antagonists. The standard options include stopping or reducing drugs, limiting dietary intake of potassium and the use of potassium-wasting diuretics. Potassium exchange resins are also an option but are typically poorly tolerated and carry a significant risk of side effects. However, several new and better-tolerated agents have been developed for this purpose and potentially may allow the continuation of drugs that would otherwise have to be stopped [89, 90]. Long-term safety and tolerability of these new drugs are however still unclear at this stage.

Device Therapy

Renal denervation (RDN) by catheter-delivered radiofrequency ablation for the treatment of resistant hypertension aims to lower blood pressure by reducing renal sympathetic activity. Although initial uncontrolled studies were very promising [91, 92], the more recently reported single-blinded, placebo-controlled Symplicity 3 trial showed no benefit of RDN over a sham procedure [93]. There is therefore some uncertainty about the true effect of denervation on blood pressure, and trials are ongoing. In the setting of CKD, there are only pilot data in small numbers of patients suggesting that RDN is safe in such patients, at least in the short to medium term, but it is difficult to be certain about blood pressure and longer term renal outcomes [94, 95]. Devices aimed at carotid baroreflex activation have also been designed and tested for the treatment of hypertension, with positive results seen in small trials, including the setting of CKD [96, 97]. Larger and longer trials are needed before the true place of these therapies in the management of resistant hypertension can be known.

Conclusions

Resistant hypertension and CKD commonly co-exist and are a dangerous combination. Out of office blood pressure measurements are vital in the diagnosis because of the high prevalence of masked hypertension and white coat effect in CKD. Treatment should involve careful attention to dietary salt reduction and medication adherence and a drug focus on diuretic titration. The evidence base is limited, and further research is needed in CKD populations to determine optimal treatments for this troublesome issue.

Compliance with Ethical Standards

Conflict of Interest Drs. Wolley and Stowasser declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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