Introduction

This document defines the current position of the ANZSN (The Australian and New Zealand Society of Nephrology) and KHA (Kidney Health Australia) in relation to the potential selection of people with treatment resistant hypertension for renal sympathetic nerve ablation (RSNA).

Hypertension is defined as blood pressure when measured in the office of 140/90mmHg and above (Chobanian 2003). Treatment of hypertension through lifestyle modification and antihypertensive medication has been shown to be extremely beneficial in lowering cardiovascular morbidity and mortality. However, some patients remain difficult to control.

Treatment resistant hypertension (TRHT)

TRHT is defined as the presence of ongoing hypertension when measured in the clinic of greater than or equal to 140/90mmHg, despite three or more medications, one of which should be a diuretic (Epstein 2007). Using this definition, the incidence of TRHT is considered to be 9-18% of the hypertensive population (de la Sierra 2011, Epstein 2007).

Should treatment resistant hypertension be defined using 24 hour ambulatory blood pressure monitoring (ABPM) and/or home self-monitoring with an ambulatory blood pressure monitor?

A number of studies have looked at the white coat or office effect in patients treated with antihypertensive medication. Data from the large Spanish registry (de la Sierra 2011) suggests that of the patients who present with office TRHT, almost two thirds (62.5%) are proven to have truly resistant hypertension with 37.5% of patients actually being controlled when assessed by ABPM. Similar rates of office or white coat hypertension were reported by Brown and Colleagues in 2001 with 28% of apparent resistant hypertensives actually controlled when assessed by ABPM. Hence approximately one third of patients who present to the office on medication with apparent treatment resistant hypertension are shown to be controlled by 24 hour ABPM studies.

ABPM remains a more accurate measure of blood pressure than office readings and it is closely aligned with target organ damage (left ventricular hypertrophy, microalbuminuria and renal impairment) and cardiovascular disease (de la Sierra 2011). The identification of a subgroup of treatment resistant hypertensive patients who in fact have controlled blood pressure when measured by ABPM over 24 hours has important ramifications for their requirement for further investigation or treatment.

Given the limited availability and expense of 24-hour ambulatory blood pressure monitoring devices, self-recording of home blood pressures with semi-automated devices
is increasingly used and correlates more closely with 24 hour blood pressure monitoring than blood pressure measured in the office (Pickering 2008, Verberk 2005). Home self-monitoring may also be more predictive of adverse outcomes than office blood pressures (Niiranen 2010).

**Refractory hypertension – definition and characteristics**

Acelajado and colleagues (2012) have characterised refractory hypertension in those patients resistant to treatment after 6 months in a tertiary referral clinic for treatment of hypertension. This group has used aggressive antihypertensive medication, lifestyle modification and the addition of spironolactone before assigning patients to the diagnosis of refractory hypertension. The treatment of any secondary causes of hypertension was allowed before such a diagnosis was made.

From their report, 9.5% of patients referred to this hypertension clinic remained refractory to treatment after 6 months of investigation and management. The characteristics of the group that remained refractory were that they had higher blood pressure at presentation, a faster resting heart rate but similar body mass index. The suggestion was made that the slightly higher resting heart rate was due to increased sympathetic activity.

**Studies using renal sympathetic nerve ablation for the management of hypertension**

To date, a limited number of studies using RSNA for the treatment of hypertension are available. The Symplicity HTN-1 Trial (Krum 2009) was a proof of concept study that demonstrated treatment using radio-frequency nerve ablation of the sympathetic nerves along the renal arteries was safe and efficacious. The Symplicity HTN-2 study (Esler 2010) randomised 106 patients to either denervation (N = 52) or control (N = 54) where the control group was assigned medical therapy. Again this study showed safety and efficacy of renal sympathetic nerve ablation with office blood pressure improvement of 32/12 mmHg at 6 months in the denervation group compared to 1/0 mmHg in the control group. However, the improvement in blood pressure following denervation in a subgroup of 20 who had ABPM was only 11/7 mmHg (Esler 2010). The EnligHTN 1 multi-electrode trial (Worthley 2013) in 46 non-randomised patients achieved a reduction in office blood pressures of 26/10 mmHg at 6 months. All patients had ABPM with a reduction of only 10/6 mmHg at 6 months. There were no acute renal arterial injuries or significant vascular complications reported.

**Current position of RSNA in the management of hypertension**

Devices employed for RSNA have obtained approval by the US Food and Drug Administration (FDA), Europe, Australia and elsewhere.
Studies demonstrating the long-term safety and efficacy of this procedure are eagerly awaited. The Symplicity HTN-1 study (Krum 2013) has revealed a sustained benefit in office blood pressures at 36 months (32/14 mmHg) in 88 patients with one new renal artery stenosis and three deaths determined to be unrelated to RSNA.

The Symplicity HTN-3 study (Kandzari 2012) commenced in September 2011 has randomised approximately 530 patients to either control treatment or renal sympathetic nerve ablation, where the control group will receive a sham procedure (ClinicalTrials.gov). The primary effectiveness outcome measure is office blood pressure at 6 months and the secondary measure is 24 hour ABPM. Results from Symplicity HTN-3 are awaited.

The safety information currently available for RSNA remains relatively short term and is based on a small number of patients in total, in comparison to drug therapy. In the above-mentioned RSNA studies, the procedure is avoided in cases with multiple renal arteries (incidence 25%, James 1962), renal artery diameter of less than 4mm, renal artery length less than 2cm, significant renal artery stenosis, previous angioplasty and/or stenting and eGFR <45ml/min. Also there are no data demonstrating any benefit with RSNA in respect to clinically important outcomes (cardiovascular events, renal failure and mortality) at this stage. Whilst this may appear likely based on the current evidence for BP reduction, this should be established before the procedure can be recommended for widespread implementation.

**Patient selection for renal sympathetic nerve ablation**

In the assessment and management of the patient with persistent office hypertension, receiving three or more agents, the following assessment is recommended prior to considering RSNA:

1. Perform 24 hour ambulatory blood pressure monitoring to exclude the white coat effect which may include approximately one third of patients presenting with TRHT.
2. Consider secondary causes of hypertension (primary hyperaldosteronism, Cushing's syndrome, phaeochromocytoma, renal arterial stenosis and glomerulonephritis).
3. Assess for contributing conditions such as obesity, sedentary lifestyle, alcohol and smoking. Assess liquorice intake.
4. Assess sodium intake using 24 hour sodium excretion and attempt to lower sodium intake to 100mmol per day (i.e. a no added salt diet).
5. Assess for obstructive sleep apnoea if suspected and treat if present (Logan 2003).
6. Assess patient compliance to treatment. This could be assessed by discussing this with the patient, obtaining a dispensing history or in some centres by measuring levels of individual antihypertensive agents (Strauch 2013).
7. Adjust the 3-agent regimen to ensure optimal doses of medication that will complement each other. In the absence of compelling indications and intolerances, the best 3-drug combination is an Angiotensin Converting Enzyme inhibitor (or Angiotensin Receptor Blocker) with a dihydropyridine calcium channel blocker (e.g. amlodipine) and/or a thiazide diuretic. The ACCOMPLISH trial demonstrated fewer cardiovascular endpoints with an ACE inhibitor + calcium channel blocker when
compared to ACEi + thiazide diuretic (Jamerson 2008). The ALLHAT Trial employed chlorthalidone (25mg) which was considered as effective as amlodipine or lisinopril (ALLHAT 2002).

8. A trial of spironolactone. In doses of 12.5-25mg daily, spironolactone has been very effective as add-on therapy in resistant hypertension with an improvement in blood pressure over 6 months of the order of 25/12 mmHg (Nishizaka 2003). The serum potassium should be monitored for hyperkalaemia especially in individuals with impaired renal function and those already receiving an ACE inhibitor or ARB.

9. Add-on drugs that block the sympathetic nervous system (neurogenic hypertension). The most effective strategy here is to combine a bioavailable beta blocker such as atenolol with an alpha-1 blocker such as prazosin (or doxazosin) (Mann 2011). Centrally acting sympatholytics (methyldopa, clonidine) can be effective but side effects can be troublesome (Mann 2011).

10. Minoxidil, a potent direct vasodilator may occasionally be useful as a last resort drug but often causes volume retention that negates the antihypertensive effect (Mann 2011). It is often poorly tolerated by women because of hirsutism and can occasionally produce a pericardial effusion.

Recommendations:

Until the results of Symplicity HTN-3 and other well conducted randomised controlled trial data are available, RSNA cannot be recommended as routine treatment for resistant hypertension by the ANZSN. However, after a comprehensive workup as outlined in “Patient selection for renal sympathetic nerve ablation” the physician and patient may wish to consider RSNA after careful consideration of the limited available data and potential risks versus putative benefits.

References:

Kandzari DE, Clin Cardiology 2012; 35(9):528-35.