Resistant hypertension, defined as BP above goal despite treatment with three classes of antihypertensives including a diuretic, occurs in up to 30% of all hypertensives. We recently saw a case that appeared to respond to the addition of spironolactone.

Discussion

Jeremy satisfied criteria for resistant hypertension. An approach to resistant hypertension includes ruling out a “white coat effect,” looking for “prohypertensive” drugs or foods (e.g., NSAIDs, licorice, cocaine), checking for non-adherence to the drug regimen and ruling out secondary causes of hypertension, including sleep-disordered breathing. None of these seemed likely in Jeremy’s case.

Jeremy’s case

Jeremy, a 36-year-old office worker, was referred for assessment of hypertension. He had been diagnosed at 22-years-old. At that time, extensive investigations including renal angiography were normal or negative. He also had asthma requiring treatment with regular inhaled corticosteroids and obstructive sleep apnea treated with continuous positive airway pressure (CPAP). His current drug regimen includes:

- Furosemide 40 mg b.i.d.
- Quinapril/hydrochlorothiazide 20/12.5 o.d.
- Minoxidil 10 mg b.i.d.
- Verapamil SR 360 mg o.d.
- Fluticasone nasal spray 100 mcg b.i.d.
- Fluticasone metered dose inhaler 125 mcg b.i.d.
- Salbutamol metered dose inhaler as needed

He denied smoking, excessive alcohol use, or drugs of abuse. His home BP readings varied from 140/90 to 176/118. Both his parents and 4 siblings are healthy. There is no family history of hypertension, diabetes or early CVD.

On examination:
- Weight 116 kg, BMI 33.2, waist measurement 121 cm
- BP averaged 151/112, heart rate 80 bpm
- Cardiac apex not displaced but enlarged and sustained, S4 present with no murmurs
- No carotid, abdominal or femoral bruits; no radial femoral pulse delay
- Trace ankle edema

For more on Jeremy’s case, see page 40.
The very high renin and aldosterone concentrations deserve comment. Renin increases with hypotension and volume depletion. Neither was operative in this case. Secondly, such a renin profile might be seen in renovascular hypertension due to renal artery stenosis. While we did not order renal artery Doppler ultrasound nor CT angiography, we believe this is unlikely. He is young, previous angiography was normal and he had no abdominal or femoral bruits. Finally, drugs can affect both renin and aldosterone. Diuretics such as hydrochlorothiazide and vasodilators like minoxidil increase renin and aldosterone. ACE inhibitors (quinapril) also increase renin but should reduce aldosterone. Unfortunately, such reduction is often temporary; ACE inhibitors reduce aldosterone initially but not long-term. This “aldosterone breakthrough” may be due to changes in the adrenal cortex itself leading to angiotensin-independent aldosterone synthesis.

We believe Jeremy manifested aldosterone breakthrough, which in turn caused his resistant hypertension. It responded to spironolactone.

In 2003, Nishizaka and colleagues reported that adding spironolactone 12.5 mg to 50 mg q.d. to the regimen in resistant hypertensives reduced BP by 21/10 within six weeks. The effect seemed independent of criteria for primary aldosteronism and additive to a ACE inhibitors, angiotensin receptor antagonists and diuretics. A subsequent study by an independent group confirmed this phenomenon, but suggested that bendroflumethiazide (a thiazide diuretic not available in Canada) was equally efficacious.

In Jeremy’s case, the effect of spironolactone was dramatic.

We continue to add spironolactone to the regimen of patients with resistant hypertension. The most common adverse effect in men is painful gynecomastia. In men with heart failure, spironolactone 25 mg to 50 mg q.d. caused breast complaints in 10%, compared to 3% with placebo. At higher doses, gynecomastia is almost universal, but often responds to tamoxifen 20 mg q.d. for one month.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The results</th>
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<tbody>
<tr>
<td><strong>Time after furosemide (min)</strong></td>
<td><strong>Direct renin U/L (normal 5-15)</strong></td>
</tr>
<tr>
<td>0</td>
<td>89.0</td>
</tr>
<tr>
<td>10</td>
<td>88.0</td>
</tr>
<tr>
<td>30</td>
<td>87.0</td>
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In men with heart failure, spironolactone 25 mg to 50 mg q.d. caused breast complaints in 10%, compared to 3% with placebo.
although not officially indicated for hypertension, causes less of this adverse effect. Both drugs can cause hyperkalemia.

In summary, spironolactone sometimes is a “wonder” drug.

The results (Table 1)

Both renin and aldosterone were elevated. We added spironolactone 50 mg q.d. to his regimen. When seen in follow-up three months later, Jeremy’s clinic BP averaged 116/73. Home readings were all < 135/85; his weight was 115 kg and his serum potassium and creatinine had not changed appreciably. He denied adverse effects from this regimen. We have been able to reduce and then stop minoxidil and furosemide.

References