Clinical Cases in Cardiovascular Medicine

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Case 1 - Mrs SD. Age 57

- Presents to GP with palpitations on and off for 4 months
  - Hypertension (BP154/96)
  - Obesity – weight 120Kg, BMI 38
  - “Mild diabetic”
  - GORD

- Drugs:
  - Inhibace plus (5mg/12.5mg) one daily
  - Omeprazole 40mg daily
Case 1 - Mrs SD. Age 57

- What next?
Case 1 - Mrs SD. Age 57

- What next?
- Triggers - Other triggers or symptoms
  - ? Stimulants – caffeine, “energy” drinks
  - exercise

- What is the palpitation?

- ECG

- Investigations
## Case 1 - Mrs SD. Age 57

### Palpitations – from the history

<table>
<thead>
<tr>
<th>Patient Symptom/description</th>
<th>Probable dysrhythmia</th>
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</thead>
<tbody>
<tr>
<td>Missed beats / bumps</td>
<td>Ectopics (atrial or ventricular)</td>
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<tr>
<td>Flutters (irregular)</td>
<td>PAF or salvoes of ectopics</td>
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<tr>
<td>Racing heart (&gt; 130/min regular) – usually of sudden onset</td>
<td>SVT - AV re-entry tachycardia, atrial flutter with 2:1 block (150/min) or VT (especially if known IHD)</td>
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<tr>
<td>Thumping heart (regular &lt;130/min)</td>
<td>Sinus tachycardia or slow VT</td>
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Case 1 - Mrs SD. Age 57

- Investigations
  - ECG – Sinus rhythm with frequent single and coupled supraventricular ectopics

- Additional tests?
## Case 1 - Mrs SD. Age 57

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
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<tbody>
<tr>
<td>FBC</td>
<td>Normal</td>
</tr>
<tr>
<td>TFTs</td>
<td>TSH 3.2 (0.6-4.5)</td>
</tr>
<tr>
<td>U+E</td>
<td>K⁺ 3.2 mmol/l</td>
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<tr>
<td></td>
<td>Na⁺ 130 mmol/l</td>
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<tr>
<td></td>
<td>Urea 7.8 mmol/l</td>
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<tr>
<td></td>
<td>Creatinine 118 mcmol/l</td>
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<tr>
<td></td>
<td>Random glucose 9.8 mmol/l</td>
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<td>HBA1c 6.9%</td>
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Another test???
## Case 1 - Mrs SD. Age 57

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<tr>
<td>Magnesium</td>
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Case 1 – Treatment Plan

- What next?
Case 1 - Treatment

- Thiazide diuretic - ? stop
  - Hypokalaemia
  - Hypomagnesaemia
  - Worsening of IGT

- Reassess the need for PPI
  - Hypomagnesaemia
  - Impairment of absorption of Iron, Calcium and B₁₂
Hypomagnesaemia

Associated with:

- Hypertension
- Impaired Glucose tolerance and diabetes
- Muscle cramps
- Arrhythmias – supraventricular and ventricular
- Impaired muscle power
- Impaired production of ATP (co-factor)
- Impaired DNA and protein synthesis
- Hypocalcaemia and reduced PTH production
- Impaired Vitamin D utilisation
- Prolonged PR, QT intervals, QRS duration, flat T waves
- Digoxin toxicity
Hypomagnesaemia - Common but ignored

- Present in 12% of hospitalized patients and 65% of ITU cases
  - Measurement – serum/plasma levels may be misleading
  - Intracellular ion; plasma level may be normal but the intracellular level low (RBC or mononuclear cell Mg^{++} expensive)

- Origins – Food (as long as it is in the soil)
  - Legumes, whole grains, nuts, green veggies, milk
Magnesium

- **PPIs??**
  - Reduced Absorption (orotic acid in small bowel)
  - pH dependant – needs acid environment
  - Gastric pH > 6-7 reduces absorption markedly

- **Diuretics** – both loop and thiazide
  - Increased losses
Magnesium supplements - Bioavailability

- NEED approx. 500mg elemental Mg per day
- Bioavailability:
  - Low < 10% absorbed:
    • Mg oxide and hydroxide (<10%)
  - Medium - approx. 40% absorbed
    • Mg chloride, citrate
    • Mg amino acid chelate
    • Mg aspartate, lactate
  - High > 60%
    • Mg orotate
Case 1 - Mrs SD

Treatment:
- Stopped diuretic and PPI
- Corrected K with supplements
- Added Mg supplements
- Palpitations disappeared

Other issues:
- Added CCB for BP control
- Diet
- Metformin for diabetes
- Statin for poor lipids
Case 2 – Mr JT age 68
Presents with:

- Continuing troublesome angina several times a day
- Muscle aches and pains especially the large muscles in the legs which he thinks is the statin
Case 2 – Mr JT age 68

- IHD
  - Anterior STEMI 2004
  - 4 x CABG 2004
  - NSTEMI 2008 – Angios:
    - Diffuse disease - stent to RCA
    - 2 x SVGs occluded. LIMA patent
  - NSTEMI 2010 Angios:
    - diffuse disease – for medical management
    - EF 30%
Case 2 – Mr JT age 68
Co-morbidities

- CCF – NYHA class II/III
- T2 Diabetes – HBA1c 9.6%
- Painful peripheral neuropathy in feet
- Hypertension
- Hyperlipidaemia
  - TC 4.6; HDL 0.8; LDL 2.4; TG 2.2
- Statin-induced myopathy with Simvastatin and struggling on with atorvastatin 10mg
Case 2 – Mr JT  age 68
Current therapy:

- Betaloc CR 95mg daily
- Atorvastatin 10 mg daily (doesn’t like it)
- Aspirin 100mg daily
- ISMN SR 90mg daily
- Inhibace 0.5 mg
- Metformin 850mg tds
- Pantoprazole 40mg daily
- Nortryptiline 25mg at night

- Allergies
  ◦ CCBs cause oedema
Case 2 – Mr JT age 68

Problems:

- Continuing troublesome angina several times a day
- Muscle aches and pains especially the large muscles in the legs which he thinks is the statin
- Painful feet
Case 2 – Mr JT age 68
What next?

- Angina
- Myopathy
- Diabetic neuropathy
Case 2 – Mr JT age 68
What next?

- Chronic Stable Angina
  - Perhexiline (needs spec. Auth)
- Morphine?
- Spinal cord stimulator?
Case 2 – Mr JT age 68
What next?

- Chronic Stable Angina
  - Allopurinol (Noman et al. Lancet June 2010)
    - 600mg (titrated gradually) daily increased exercise capacity and walking time by 25% (p=0.0002)
    - Allopurinol protects heart from oxygen deprivation
Case 2 – Mr JT age 68
What next for Statin Myopathy

?
Case 2 – Mr JT age 68
What next for Statin Myopathy

- Ezetimibe
- Fibrates
- Nicotinic acid
- Co-enzyme Q10
- Red Yeast Rice
Case 2 – Mr JT age 68
What next for Statin Myopathy

- **Ezetimibe:**
  - Lowers LDL by 18% BUT No outcome evidence for benefit

- **Nicotinic acid** (Taylor et al. NEJM. November 2009)
  - Niacin LA (Niaspan) 2000mg + low dose statin caused significant reduction in carotid atheroma vs. Statin + ezetimibe (actually worsened)

- **Fibrates**
  - Can cause myopathy and much less effective than statins
Co-enzyme Q10
- Helps to reduce myopathic symptoms
- Conflicting reports from small studies

- Lovastatin monocolins isolated
- Patients with statin myopathy
- 1800mg-2400 mg daily reduced LDL by 22% (similar to pravastatin 20mg)
- No muscle problems
Case 2 – Mr JT age 68
What next for diabetic neuropathy?

- Anti-epileptic drugs
  - Carbamazepine / Gabapentin

- Alpha-lipoic acid – powerful thiol antioxidant – central to antioxidant defence of brain and nervous system
  - R-DB-PC trial in distal symmetrical neuropathy
  - 600mg daily → 62% reduction in total symptom score (pain, burning, numbness) score after 5 weeks (p<0.05). (Ziegler D et al. Diabetes Care. 2006;29:2365-70)
Case 3: The Hypertensive Middle Manager

- 43 yr old male middle manager in IT company
- Hypertension – BP average over 6 readings 162/90
- Father had MI at 66
- Overweight (BMI 30)
- GORD
- Alcohol approx. 30 units / week
- Non-smoker 6-months
- Exercise – plays squash once a week
Hypertensive Middle Manager

What do you do next?

Risk factor profiling:
- Lipids
- Fasting glucose
- Renal function
- Na/K/Mg
- ECG
Risk factor profiling:

- Lipids – TC 5.9; HDL 0.9; LDL 4.2; TG 2.6
- Fasting glucose – 5.9mmol/l
- Renal function – Urea 6.9; Creatinine 96
- Na/K/Mg – 138/3.8/0.72
- ECG – normal
Cardiovascular Risk Score

- 5 - year risk
Cardiovascular Risk Score: 5 – year risk

- 10-15%

- Recommendation:
  - Smoking cessation
  - Non-pharmacological treatment to reduce risk
Lifestyle and Nutraceuticals

- Exercise
- Weight loss
- Nutrition and specific nutrients
- Vitamin D
- Moderate intensity (40-70% VO2 max) for 30-60 minutes 5-7 x weekly
- > 70% VO2 max has no additional effect on BP

- ?? The non-dippers are the non-responders
Non-dippers – Increased target organ damage – heart and kidneys

> 10% fall in mean BP overnight
**When to exercise?**

*Park et al.*
*Journal of Human Hypertension* 2005;19(8):592-605

<table>
<thead>
<tr>
<th><strong>DIPPERS</strong></th>
<th><strong>Non-DIPPERS</strong></th>
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<tbody>
<tr>
<td>Exercise anytime reduced average BP but not the mean nocturnal BP</td>
<td>Daytime exercise reduced mean BP</td>
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<tr>
<td></td>
<td>Evening exercise reduced nocturnal BP very significantly</td>
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**Message**

Non-dippers should exercise in the evenings

Dippers exercise anytime
# Additional Benefits of Exercise


<table>
<thead>
<tr>
<th>Moderate Exercise (40-70% VO2 max)</th>
<th>Heavy Exercise (&gt; 70% VO2 max)</th>
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<tbody>
<tr>
<td>Reduced platelet adhesiveness</td>
<td>Increased platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Increased platelet count</td>
</tr>
<tr>
<td>Increased fibrinolysis</td>
<td>Increased fibrinolysis</td>
</tr>
<tr>
<td>Coagulability unchanged</td>
<td>Increased Coagulability</td>
</tr>
<tr>
<td>Reduction in LV hypertrophy</td>
<td></td>
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<tr>
<td>Reduced oxidative stress</td>
<td></td>
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<tr>
<td>Increased NO availability</td>
<td></td>
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<tr>
<td>Improved metabolic profile</td>
<td></td>
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<tr>
<td>Improved exercise capacity</td>
<td></td>
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<tr>
<td>Improved QoL</td>
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Then... Now

Food
Average volume of soft drink consumed per person per year in Australia in the 1970s and in the 2000s:
- 47 litres
- 113 litres

Fast food burger fat content is twice level of 20 years ago:
- 12-24 grams
- 24-42 grams

Portion Size
Standard packet of chips size in 1970s and now:
- 30 grams
- 50 grams

Inactivity
Increase in number of cars driven to work each day in Australian capital cities between 1976 and 2006:
- 70% (more than 1.4 million cars)

Fat Nation
Motto: Our girth is plain to see

- Weight loss of > 6.8Kg reduced risk of developing hypertension by 21-29%

- Sustained (>4 years) weight loss reduced hypertension risk by 22% in middle-aged and 26% in older adults

Modest weight loss, particularly when sustained, substantially lowers the long-term risk of hypertension in overweight adults
Weight loss facts

- Every 1% Weight ↓ = 1 mmHg ↓ BP.

- Weight-reducing diets:
  - 3–9% decrease in body weight
    - reduces SBP + DBP by 3 mmHg.
  - Losing 4.5 kg
    - reduces blood pressure or prevents hypertension in a large proportion of overweight people
  - Losing 10 kg
    - can reduce systolic blood pressure by 6–10 mmHg.
Weight Loss and Hypertension

- Obesity, Diabetes, Hypertension and the metabolic syndrome are associated with **elevated levels of inflammatory cytokines and Excess Free Radicals**

- Weight loss by however achieved:
  - Dramatically reduces inflammation as measured by CRP
What diet is best, Doc?

- Low fat / high carb? – Worsens cardiovascular risk factors
- High protein / low carb? – Atkins-type
  - Improves lipid profile but difficult to sustain
- Palaeolithic – not studied in depth
- Mediterranean
  - Improves insulin sensitivity
  - Improves lipid profiles
  - Reduces BP
  - Reduces cardiovascular risk
The Mediterranean diet

Daily Beverage Recommendations:
6 Glasses of Water

Weekly:
- MEAT
- SWEETS
- EGGS
- POULTRY
- FISH

Monthly:

Daily:
- OLIVE OIL
- CHEESE & YOGURT
- FRUITS
- BEANS, LEGUMES & NUTS
- VEGETABLES
- BREAD, PASTA, RICE, COUSCOUS, POLENTA, OTHER WHOLE GRAINS & POTATOES

Daily Physical Activity
Olive oil, the Mediterranean Diet and arterial BP.

- 20,343 participants in the Greek EPIC Study (European Prospective Investigation into Cancer and Nutrition)
- 10-point score of adherence to MD
  - Effect of individual components and Olive oil
- Diet score significant inverse association with both systolic and diastolic BP
  - Olive oil, vegetables and fruit – inverse risk
  - Cereals, meat and meat products positive correlation with risk
- Olive oil had dominant effect overall on BP
Mediterranean Diet and Incidence of Hypertension
(Hypertension 2009;54:1143-1150)

- 9,408 men and women enrolled 1999-2005 in prospective cohort study
- 9-point MD score
- Median follow up 4.2 years
  - Systolic BP reduced by 2.4mmHg in moderate adherence and 3.1 in high adherence
  - Diastolic BP reduced 1.3mmHg in moderate and 1.9mmHg in high adherence after 6 years follow up
23 Hypertensive patients - Randomised double blind crossover study
  ◦ Extra Virgin Olive oil (MUFA) vs. Sunflower (PUFA)

Resting BP was significantly lower at the end of the MUFA diet compared with the PUFA diet (P = 0.05 for systolic BP; P = 0.01 for diastolic BP)
Daily drug dosage was significantly reduced during the MUFA but not the PUFA diet (-48% vs. -4%, P<0.005).

All patients receiving the PUFA diet required antihypertensive treatment,

8 of those receiving the MUFA diet needed no drug therapy.
Endothelial Dysfunction and Hypertension


- Key role in vascular complications of diabetes and hypertension.
  - ↓ Endothelium-derived NO synthesis

- Exaggerated production of vasoconstrictors
  - Angiotensin II, endothelin-1, reactive oxygen species, cyclooxygenase-derived metabolites of arachidonic acid

- Specific therapies:
  - target Renin-angiotensin system
  - Increase NO synthesis
  - Antioxidants vs. Reactive oxygen species
Magnesium – the forgotten mineral

- Epidemiologically inverse relationship with Mg intake and BP
- Cellular depletion contributes to LVH, insulin resistance, obesity and Type 2 diabetes, arrhythmias
- Intracellular Magnesium deficit (NMR spectroscopy) in human hypertension
34 male and 26 female Japanese hypertensives
8 weeks supplementation Mg oxide 480mg

Systolic and diastolic BPs fell significantly
Those with highest BP had greatest falls

Other trials give a mixed picture
Magnesium and Hypertension
Points of interest

- Universal intracellular deficit of Mg
- Serum Mg values can be within the normal range
- Proper patient selection
  - Patients with high or normal Renin have low intracellular and serum magnesium levels
  - Normal or High Renin predicts response to Mg
Vitamin D and Hypertension

- Vitamin D → Liver → 25(OH)D → Kidney
- Prostate Gland, Breast, Colon, Lung Immune Cells
- 1,25(OH)2D → Calcium, Muscle, Bone Health & Regulation of Blood Pressure
- Insulin Production (heart disease and diabetes prevention)
- Regulation of Immune Function (diabetes type 1, MS, RA autoimmune disease prevention)
- Regulation of Cell Growth (cancer prevention)

Sources: Milk, Orange Juice, Salmon, Supplements
Vitamin D and Hypertension

- Vitamin D
  - renoprotective effects
  - suppression of the renin-angiotensin-aldosterone system
  - direct effects on vascular cells
  - effects on calcium metabolism, including prevention of secondary hyperparathyroidism
1484 women aged 32-52 yrs without hypertension
  ◦ Nested case-control study
Median 25OH-D level 64nmol/l (controls 68nmol/l)
Lowest vs. highest quartile of Vitamin D - OR of developing hypertension 1.66 (1.11-2.48)
Vitamin D level < 75nmol/l had multivariable OR 1.47 for developing hypertension
• 18 patient with mild untreated hypertension (age 26-66)
• UVB vs. UVA 3 x weekly for 6 weeks
• 162% increase in Vitamin D (UVB)
• Significant fall in both systolic and diastolic day and night-time BP

The Lancet 1998; 352:709-710
Can Vitamin D supplementation treat or prevent hypertension?

- Trials are conflicting
- Levels of supplementation were low and the levels of plasma Vitamin D achieved barely reached the minimum level now regarded as indicating sufficiency (75nmol/l)
- Big interventional trials needed aiming to achieve levels > 75 nmol/l
Co-Enzyme Q 10 – conflicting results
Hawthorn – unclear. Does help in heart failure
Pycnogenol
Grape seed extract – (works in rats)
Tomato Extract
Melatonin
Nutraceuticals and BP

  - 58 pts with mild hypertension – 100mg daily over 12 weeks
  - Significant reduction in Nifedipine dosage achieved
  - Significant decrease in endothelin-1 level
Tomato Extract - R-PCT, double-blind crossover (Paran E et al. Cardiovasc Drugs Ther. 2009;23:)

- 50 poorly controlled hypertensive patients already on variety of drugs
  - Automatic BP measurements
  - Lyc-O-Mato 250mg daily
  - Reduction of 13/4 mmHg vs. Placebo
  - Reduced lipid peroxidation products

- Flavonoids - Lycopene, quercetin, rutin
  - Antioxidants
    - Protects NO from degradation by oxygen free radicals

- Polyphenols
  - Increases l-arginine availability (rate-limiting factor in production of NO)
Melatonin in Hypertension


- 38 treated hypertensives (non-dippers)
- RDBPCT
- SBP reduced (p=0.01)
- DBP reduced (p=0.002)
- Most prominent between 2.00 AM and 5.00AM
The use of current drug therapies
  ◦ What adverse effects are we ignoring?
    • Magnesium and potassium deficiency in diuretic use
    • Magnesium deficiency with PPIs

Many unanswered questions and need for interventional trials:
  ◦ Adequate Vitamin D – an exciting prospect in many facets of Medicine
  ◦ Antioxidants – a target for new drugs?