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SLEEP APNOEA

SLEEP APNOEA AND ITS ASSOCIATION WITH CARDIOVASCULAR DISEASE

Sleep apnoea is very common among the general public and has been estimated to affect as many as one in three Singaporeans. The condition is often overlooked and not considered by doctors unless patients or their spouses specifically complain about excessive snoring or daytime sleepiness. However, if present, sleep apnoea increases cardiovascular risk and is associated with increased morbidity and mortality. Hence it is important that doctors consider this diagnosis when reviewing patients and take active measures to confirm the diagnosis and treat the condition as appropriate. The most common type is obstructive sleep apnoea (OSA) which is associated with obesity and a short neck. In OSA, there is collapse of the pharynx during sleep with subsequent upper airways obstruction that leads to excessive snoring and the classic apnoeic episodes. The other form of sleep apnoea, central sleep apnoea (CSA), is much less common and is usually associated with heart failure; it has also been observed in patients with stroke, renal failure and with opiate use.

The effects of sleep apnoea on cardiovascular health
Sleep apnoea is a recognised cause of secondary hypertension. OSA episodes result in surges in systolic and diastolic pressure that keep the mean blood pressure levels elevated at night. In many patients, blood pressure can also remain elevated during the day, even though breathing is normal. In such patients, the blood pressure can be hard to control, even with multiple antihypertensive medications, unless the underlying problem is identified and corrected. Sleep apnoea is also associated with several other cardiovascular conditions, including heart failure, cardiac arrhythmias and sudden cardiac death. The relationship between sleep apnoea and cardiovascular pathophysiology is still not completely understood, although observational studies suggest that treating sleep apnoea can greatly improve cardiovascular outcomes. For example, atrial fibrillation can be harder to control and manage in patients with OSA and the results of catheter ablation are improved if the sleep apnoea is treated successfully. Thus, international guidelines suggest that it is worthwhile to screen for this condition. [Ann Intern Med. 2014 Aug 5;161(3):210-20]

How is sleep apnoea diagnosed and quantified?
Sleep apnoea should be suspected if patients exhibit typical symptoms such as excessive daytime sleepiness, insomnia, morning headaches, depression, cognitive dysfunction, nocturnal dyspnoea, nocturia, and erectile dysfunction. However, there is a wide variation in symptoms, especially between men and women, so the combination of some of these symptoms with other medical issues, such as poorly controlled hypertension should alert the clinician to the possibility of sleep apnoea.

It should be noted that not all patients with sleep apnoea exhibit these typical symptoms. Patients with heart failure and sleep apnoea do not tend to complain of daytime sleepiness, possibly related to high sympathetic tone. Thus screening questionnaires that include questions about daytime sleepiness (such as the Epworth Sleepiness Scale used to screen for OSA in non-heart failure populations) are not useful in patients with heart failure.

The gold standard method to diagnose sleep apnoea is via in-hospital polysomnography (PSG), during which parameters such as respiratory movement, oxygen saturation, nasal and oral airflow, ECG, EEG, EMG and ocular movements are measured and analysed. However, this test requires an overnight stay in hospital, which may not be readily accessible for many patients and is expensive. Thus, portable devices have been designed to diagnose OSA which are more convenient and can be set up in the patient's home. Type II monitors use at least 7 channels (compared with 14 - 16 channels in PSG) and measure the same physiological variables as PSG. Type III monitors have only 4 or more channels and measure airflow, heart rate, and oxygen saturation. Even simpler screening may be performed by recording nocturnal oxygen saturation via a finger probe, although such screening cannot determine the type and severity of sleep apnoea and further investigation is required in those who test positive and in anyone who tests negative but where clinical suspicion remains high.

The severity of sleep apnoea is described by the average number of apnoeic and hypopnoeic events per hour of sleep—the apnoea-hypopnoea index (AHI). Up to 5 events per hour is usually defined as normal, 5–15/hour as mild, 15–30/hour as moderate, and >30/hour as severe sleep apnoea.

Management of sleep apnoea

1. General advice and lifestyle measures- Patients should be given general lifestyle advice such as losing weight if they are overweight or obese, stopping smoking, limiting alcohol consumption and avoiding caffeine, particularly before going to bed. In addition, sedatives and sleeping tablets should be avoided as they may reduce upper airway muscle tone. Sleeping on one's side rather than the back and developing a pre-bedtime routine such as taking a warm bath, dimming the lights or having some herbal tea may help some patients.

2. Optimisation of medical treatment- Optimal medical management is likely to improve sleep apnoea and should not be overlooked. This may include the use of diuretics and disease-modifying therapy such as ACE-inhibitors/ARBs, beta-blockers, and aldosterone antagonists in patients with heart failure. Studies have also show that cardiac resynchronisation therapy (CRT) for patients with heart failure with reduced ejection fraction and a broad QRS complex significantly reduces AHI in CSA (but not OSA). Patients with frequent troubling arrhythmias, such as atrial/ventricular ectopics or atrial fibrillation, and sleep apnoea may require specific anti-arrhythmic medication (such as beta-blockers or sotalol) to limit the symptoms due to the arrhythmia whilst receiving treatment for the sleep apnoea.

3. CPAP devices and surgery- As well as the lifestyle changes, people with moderate to severe OSA may need to use a continuous positive airway pressure (CPAP) device. CPAP treatment can reduce symptoms such as snoring and tiredness ad can also reduce the risk of complications of OSA, such as high blood pressure. However, a recent randomized study involving 2717 patients with moderate to severe OSA failed to show that therapy with CPAP plus usual care, as compared with usual care alone, prevented cardiovascular events in patients with established cardiovascular disease [McEvoy RD et al. N Engl J Med. 2016 Sep 8;375(10):919-31]. In severe forms of OSA, surgical treatment such as uvulopalatopharyngoplasty may be required.

In summary, sleep apnoea is very common, especially among patients with cardiovascular risk factors or established cardiac disease. The condition should be actively considered and confirmed and appropriate treatment recommended to reduce cardiovascular morbidity and mortality. Simple lifestyle advice may be sufficient in mild cases, although more severe forms may require the use of CPAP devices or surgical intervention.

By **Dr. Reginald Liew**
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LIFESTYLE MEDICINE

LIFESTYLE MEDICINE, WHAT EVERY DOCTOR SHOULD BE PRACTICING

Lifestyle medicine, one of the best medicines
Heart disease and stroke collectively is the number one killer in the world, and a leading cause of disability. Imagine if we can eradicate almost 90% of these conditions without medication or surgery, sound too good to be true? It's not! The impact of healthy lifestyle changes has been scientifically proven to not only prevent, but also treat many chronic diseases, yet this still remains a little known fact. As part of its 2020 impact goals, the American Heart Association has set out seven ideal health metrics: absence of smoking, a normal body mass index (BMI), physical activity, a healthy diet, normal cholesterol, normal blood pressure, and normal fasting plasma glucose.[1]. An analysis from the National Health and Nutrition Examination Survey showed that individuals who met five of the seven ideal metrics had a 78% lower chance of dying from any cause [2]. A healthy diet can also decrease the risk of developing diabetes [3], high blood pressure [4], and heart failure [5]. "There is no pill, and there never will be any pill, that can reduce the burden of chronic disease in the way that healthy lifestyle factors can," says Dr. David Katz, director of the Yale University Prevention Research Center and past president of the American College of Lifestyle Medicine. "There's almost nothing in all of medicine that has the vast, consistent, and diverse evidence base."

What exactly is lifestyle medicine?
Lifestyle medicine is a scientifically proven branch of medicine that harnesses the therapeutic power of lifestyle to prevent, treat and even reverse lifestyle-related chronic diseases. Instead of conventional drug treatments, the focus is on physical activity, nutrition, stress management, adequate sleep, social support, tobacco and alcohol cessation, and other non-drug modalities. Exercise and food can be used as medical therapies, but the appropriate type and dose for individuals need to be tailored in order to yield optimal health. Modern medical treatments often do not treat the root causes of disease. Recognizing this, lifestyle medicine has evolved into a recognized medical specialty in its own right. Lifestyle medicine practices such as Ornish lifestyle medicine, Cleveland clinic integrative and lifestyle medicine; and International and National medical societies such as the European society of lifestyle medicine, American College of Lifestyle Medicine and the Preventive and Lifestyle Medicine Society of Singapore have been formed to address this deficiency.

Cardiatrics - collaborating with GPs to deliver preventive cardiology
Cardiatrics is a first of its kind, cardiovascular disease prevention and therapeutic program that incorporates lifestyle medicine. Through their medically supervised Cardiatrics program, The Harley Street Heart and Cancer centre collaborates with general practitioners (GPs) to promote therapeutic lifestyle changes in their patients in order to improve clinical outcomes and quality of life. The program is modeled after proven scientific programs such as cardiac rehabilitation and the diabetes prevention program. It is delivered through an interdisciplinary network of allied health professionals including nurses, dietitians, exercise specialists and psychologists that will work virtually with the GPs to promote sustainable healthy lifestyle modifications leading to risk factor reduction and even disease regression. Cardiatrics comprises a comprehensive cardiac risk assessment that goes beyond conventional risk markers to include in-depth assessment of a client's routine lifestyle to identify areas that need improvement, after which specific customized recommendations can be instituted. There is also a four-month intensive optimization program to treat and reverse coronary artery disease and its risk factors. Cardiatrics allows GPs access to specially designed and supervised medical therapeutic programs; as well as multidisciplinary team and medical specialist support without incurring any additional cost or manpower of their own.

What are the benefits and who should participate?
Ideal patients include anyone with one or more of the following: 1) hypertension, 2) high cholesterol, 3) clinical obesity (particularly abdominal obesity), 4) early or pre-diabetes, metabolic syndrome, 5) family history of premature heart disease, 6) poor lifestyle habits including smoking or excessive alcohol 7) suboptimal cardiorespiratory fitness, 8) male age > 40yrs old, female > 50yrs old 9) subclinical atherosclerosis (e.g. raised calcium score or carotid intimal medial thickness). The more risk factors they possess, the more urgent the need for therapeutic lifestyle interventions. Lifestyle medicine when administered early can significantly alter a person's vascular and general health trajectory, often without the need for medication. Clients are paired with a dedicated Cardiatrics doctor and coach supported by the healthcare team. They will receive personalized lifestyle interventions based on their individual medical conditions, abilities, preferences and environmental/social circumstances. Possible benefits include improvement of blood pressure, cholesterol and blood sugar levels; optimization of weight and body fat composition, improving fitness and energy levels; reducing reliance on medication and medical costs in the long term.
In the past, structured prevention programs could only be delivered in large institutional practices with access to multidisciplinary expertise. Now with modern technology, enhanced connectivity and monitoring, GPs can now also deliver cost effective prevention programs to enhance the lives of their patients. With Cardiatrics, therapeutic lifestyle interventions can and should be accessible to every patient as first line treatment for any chronic disease related to poor health habits. It is one of the best treatments available that we can no longer afford to ignore.

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HEART AND KIDNEY FAILURE

HEART FAILURE AND KIDNEY FAILURE : IS THERE A LINK?

Life expectancy in end-stage renal failure (ESRF) patients is poor despite modern dialysis and medication. This is mainly due to pre-existing or new onset cardiovascular disease (including heart failure, ischemic heart disease and stroke) in such patients. Besides the "conventional" cardiovascular risk factors, recent evidence points to other causes found in chronic kidney disease (CKD) patients that may account for the pre-mature death. These include uraemia, arteriosclerosis with "accelerated atherosclerosis", vascular calcification, renal bone disorder and others.

Heart disease is found in 30-40% of CKD patients. One-quarter of these has congestive cardiac failure (CCF) mainly due to underlying ischemic heart disease. As kidney function worsens, the prevalence of CCF increases and at stage V CKD (ESRF), 60-70% of CKD patients will have CCF. There is mounting evidence that CKD itself is a major contributor to severe cardiac damage and, conversely, that CCF is a major cause of progression of CKD. Poorly controlled CCF is often associated with a rapid fall in kidney function; this can be attributed to compromise renal perfusion, salt and fluid retention, systemic and intrarenal vasoconstriction and neuro-hormonal activation seen in cardio-renal syndrome. Trials have shown that adequate control of CCF can prevent or retard CKD progression. The opposite is also true : optimal treatment of CKD can prevent or improve CCF.

Three common factors have been identified to interact closely between CCF and CKD :

1. Anemia
   - Anemia is seen in about 70% of CKD and one-third of all CCF cases. Anemia is associated with worsening heart and renal function and often with signs of malnutrition. CKD can cause anemia due to low erythropoetin production and iron deficiency; this in turn will stress the myocardium and worsen heart function.

2. Hypertension
   -Uncontrolled blood pressure (BP) acts in a vicious cycle to worsen renal function as well as heart function.

3. Fluid balance
   - CKD can be complicated by fluid overload which will worsen cardiac function and hence decrease ejection fraction. However, over-diuresis using high dose diuretics can reduce intra-vascular volumn, compromise renal perfusion and make the kidney function worse.

Management of CKD and CCF

Blood Pressure
Optimal BP control can reduce risk of cardiac and renal failure. Eighth Joint National Committee (JNC8) recommends treating BP to goal of SBP <140 mmHg and DBP <90 mmHg for both CKD and CCF patients. Angiotensin converting enzymes inhibitors (ACE-I) or angiotensin receptor blocker (ARBs) is still the preferred anti-hypertensive medication of choice.

Anemia
The appropriate target for hematocrit and hemoglobin to minimise left ventricular hypertrophy or cardiac death has not been defined. KDOQI guideline recommends keeping hemoglobin between 11-13 g/dL. Use of hematinics and erythropoetin-stimulating agents are often required to correct the anemia.

Fluid Balance
Diuretics is commonly used for symptomatic fluid overload. Doses of diuretics should be titrated downwards to the lowest possible dose once asymptomatic to avoid over diuresis and rising creatinine.

Optimal Control Of "Conventional" Cardiac Risk Factors
Bringing associated risk factors such as hyperlipidemia and diabetes to target. Healthy (low salt, low fat) diet.

Correction Of CKD Complications
All electrolytes, acid-base imbalance, renal bone disease associated calcium and phosphate abnormalities need to be corrected to minimise insults on cardiac function.

In summary, many factors inter-connect CCF and CKD. Optimal control of CCF will improve CKD outcomes; the converse is true. Cooperation and collaboration between cardiologists and nephrologists in management of such patients will improve quality of care and subsequent prognosis for both CCF and CKD.

By **Dr. Roger Tan**
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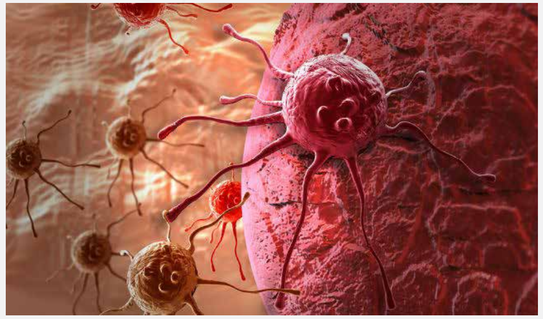
IMMUNOTHERAPY

DOES TARGETED THERAPY AND IMMUNOTHERAPY REPLACE CHEMOTHERAPY IN THIS ERA OF PERSONALISED MEDICINE?

The advent of genetic mutation testing and to a lesser extent, next generation sequencing (NGS) of cancer cells in any particular has given rise to the concept of personalized medicine, where treatment is tailored towards that particular cancer in that particular patient. Hence the name targeted therapy. Yet, despite the identification of the specific targets, a percentage of patients still do not respond to the treatment.



In the example of non-small cell lung cancer, the epidermal growth factor tyrosine kinase inhibitors (EGFR TKIs) supposedly target the EGFR mutations in the cancer cells. In the phase III trials, response rates had been reported between 50-70%. Why not 100%? It is known now that there are mutations that are primarily resistant to inhibition of a TKI. Is it also possible that there are other co-existing mutations which will become the driver of the cancer growth while the EGFR is being inhibited, such as ALK or MET mutations.

Immunotherapy has been approved 2 years ago as standard treatment for lung cancers. Its biomarker, PD-L1, can be demonstrated on immunohistochemistry staining of the biopsy specimen. Increasingly, trials have shown that the higher the level, the higher the response rate to treatment. However, about 75% of all lung cancers have less than 50% PD-L1 staining. Indeed, initial trials have shown that the maximal response rates that could be achieved were about 40% in unselected population. Even in highly selected population with PD-L1 greater than 50% positivity, the response rate could reach 80%.

The literature has shown that despite having a 'target' or biomarker to select specific lung cancer patients for select highly targeted treatment, the results are far from optimistic for the subpopulation who does not respond well. Very often, we can early progression within first couple of months with worsening symptoms, necessitating a change in treatment to chemotherapy, which is less 'targeted' yet had been shown to produce response rates albeit in the lower range.

Patients who develop severe toxicities from targeted and immunotherapies, will also have to discontinue treatment, even if the treatment is working remarkably well. Often, very deranged liver function test or development of pneumonitis may cause more harm if the treatment is restarted when the toxicities resolved. These patients will also need to fall back on chemotherapy for control of their disease.

The examples given are in the lung cancer population, but this is the same scenario for other cancer types. Chemotherapy remains an important modality despite modern advances. Patients are living longer and increasingly unresectable cancers are turning into chronic diseases. The treatment continuum in each patient will be different and personalized medicine is still very much the order of the day. It will mean chemotherapy may initially take a backseat for some patients but it cannot be ignored completely in the quest for prolonging cancer patient survival.

By **Dr. Ooi Wei Seong**

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BREAST CANCER

CHANGING PARADIGM IN THE TREATMENTS OF BREAST CANCER

For many years, Breast cancer has always been treated an as entity. The treatment paradigm for early breast cancer has always been surgery followed by chemotherapy and radiotherapy. However, with the advancement of molecular biology, we can now classified breast cancer into 4 main groups. This classification enables surgeons and oncologists to tailor treatments to each individual patient, allowing less side effects from unnecessary treatments and providing better treatment outcomes. The sub-groups are classifies by the receptor status (ER/PR/Her2), mitotic grades.

The 4 main groups of breast cancer are:

1. Luminal A-tend to be ER/PR +ve, Her2 –ve, low grade tumours. About 30-70% of breast cancers are Luminal A. Tumours respond to hormonal therapy and has the best prognosis among the 4 sub-types. For early breast cancer

2. Luminal B-tend to be ER/PR+ve, may be Her2+ve or -ve, high grade tumours. Women tend to be younger at diagnosis. Around 10-20% of breast cancers are Luminal B type.

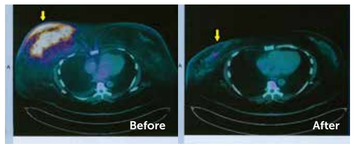
3. Triple negative tumours are tumours with no receptors, these tumours tend to be aggressive, and spread to vital organs early. Around 15-20% of breast cancers are triple negative. Although it is associated with poor prognosis, some triple negative breast cancers can be treated successfully.

4. Her2 +ve are tumours with Her2 receptors. About 20% of breast cancers are Her2 +ve. Her2 positive breast cancer can be treated with Her2 targeted therapy. Before these drugs were available, Her 2 +ve breast cancers had poor prognosis.

Until the 1990's, treatment paradigm for early breast cancers has been surgery, followed by chemotherapy and radiotherapy. With the development of neo-adjuvant chemotherapy, the treatment paradigm has been changed according to the sub-type of breast cancer. Neo-adjuvant chemotherapy was initially designed to convert un-resectable tumours into operable tumours, and downsizing tumours for conservative surgeries. As the sub-types of breast cancer become more defined, oncologists have identified the sub-types of breast cancer that are most likely to respond to neo-adjuvant chemotherapy, these are the triple negative breast cancers and the Her2 +ve breast cancers. Current data show that neo-adjuvant chemotherapy prolongs the disease free intervals, although there is no data on improve overall survival at this moment. So neo-adjuvant chemotherapy for these 2 sub-groups are often recommended.

In summary, with the advancing knowledge in the molecular sub-types of breast cancers, surgeons and oncologists are working closely together to form the best treatment paradigm for each individual patient, oncologists are working closely with pathologist to best define the sub-type of breast cancer in order to provide a tailor systemic therapy to each individual patient.

Picture showing a locally advanced Her2 +ve breast cancer responded to neo-adjuvant chemotherapy.



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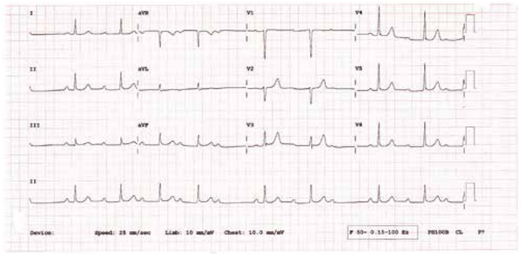
ECG QUIZ



Case Vignette:
This 53 year old lady was referred for recurrent and increasingly frequent presyncope.

What is the diagnosis and how would you investigate further?

Answer is available on our website:
http://www.harleystreet.sg/quiz-answers/medbulletin-mar-2017/

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THE HARLEY STREET HEART & CANCER CENTRE

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THE HARLEY STREET HEART & CANCER CENTRE

From left to right:
Dr. Sue Lo, Dr. Reginald Liew, Dr. Peter Ting, Dr. Ooi Wei Seong, Dr. Rohit Khurana

INTRODUCTION

Greetings from the Harley Street Heart and Cancer Centre! We are pleased to present our first newsletter of 2017 in which we aim to provide the busy clinician with practical updates on the latest advances in the fields of cardiology and oncology.

In this edition, our cardiologists provide some articles on common lifestyle related issues that can greatly impact our patients' lives if successfully identified and corrected. Dr. Peter Ting provides an article on the latest ideas in preventative cardiology and Dr. Reginald Liew provides an overview of the current understanding and recommendations in patients with sleep apnoea and cardiovascular disease. Dr. Ooi Wei Seong discusses the current and future roles of targeted therapy and chemotherapy, especially in patients with lung cancer, whilst Dr. Sue Lo provides an update on the changing paradigm in the treatment of breast cancer. Our guest article, written by renal physician, Dr. Roger Tan, is on the association between heart failure and kidney failure, two very common conditions affecting many of the patients we look after.

We hope these articles stimulate and challenge your views on the latest ideas in the treatment of heart disease and cancer. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

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