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Dealing with the Changing Disease Pattern and Management in Paediatrics & Cardiology

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The contents of this issue include both common paediatric and cardiologic problems. The cardiology part is a continuation of the previous issue and it reflects the high disease burden related to this specialty and the mounting medical resources being invested into this major adult morbidity domain. New technology in both diagnosis and intervention keeps emerging from this area. We are delighted to have the great support from our cardiology colleagues and their willingness to share their knowledge with us.

On the other hand, the dropping in birth rate (only 0.73 birth/couple) in Hong Kong has a significant impact on the paediatric population. The local paediatric population has been shrinking gradually and so does the investment and resources for the medical care on children. The eventual negative impact on the future medical care of paediatric patients is worrisome. Despite the potential future challenge of trimming resources, there has been indisputable improvement in the healthcare for children locally for the past 2 decades. We all witness a major shift in the diseases incidences and decrease in childhood mortality within this period. Through the successful implementation of universal vaccination programme and effective treatment of infection, infectious diseases contributed to a much smaller proportion in the paediatric morbidity and mortality currently. Interestingly, new infections continue to emerge and will keep us alert all the times. However, their relative significances have been replaced by the increase trends in allergy related illnesses.

Allergy related illnesses are the commonest disease category in both private and public paediatric clinics nowadays. Our allergy and paediatric experts are sharing with us their views about how to prevent and treat allergy in children. That includes the hypothesis of allergy prevention, and the current thoughts on the management of food allergy and eczema. These are comprehensive reviews which can help to provide updated medical advices and management to our patients in the clinic.

Another common paediatric problem is haemangioma. It is the commonest childhood tumours and the nomenclatures had been confusing and did not provide any guidance to the treatments in the past. There have been changes in the diagnostic classification and management approaches for childhood vascular anomalies in recent years and a brief review is provided.

In this issue of brief review on the changing disease pattern and management in paediatrics & cardiology, we hope that we can provide you with useful information for your daily practice.

Clinical Management of Childhood Food Allergy

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Childhood Food Allergy

There is an upsurge in demand of clinical service in the management of childhood food allergy in almost every developed place. Certainly, Hong Kong is of no immunity. Is food allergy a growing problem or is it just a diagnostic fashion? I believe that we are looking at a combination of 1) increased rates of sensitisation 2) increased likelihood of sensitisation progressing to disease 3)increased recognition of food allergy 4) increased use of medical services or a change of health seeking behaviour. Food allergy is a huge subject. There are vast diversities in pathogenesis, clinical presentations, cultural and racial variations and many unresolved controversies. In this review, I will try to focus only on some of the core knowledge that we would apply in our daily clinical care.

Key Concepts

- The prevalence is greatest in the first few years of life. (5% to 8% of children in their first year of life).
- Relative few foods account for about 90% of food allergy (milk, egg, peanut, nuts, soy, wheat, and fish).
- Milk allergy at 1 year of age is a risk factor for additional food allergies in later childhood.
- Food hypersensitivity in early life is found to be a risk factor for atopic dermatitis, and later asthma.
- Food allergy should be differentiated from adverse reactions to food due to non-immunological mechanism

Case Scenario

Tom, a 14-month-old boy was born after an uneventful pregnancy and delivery. He was exclusively breast fed for 5 months. The mother had unrestricted diet. Eczema developed from 6 to 8 weeks of age. His mother noted at the age of 9 months egg caused a local urticarial reaction on the face and at the age of 10 months less than a quarter of teaspoon of peanut butter produced immediate angioedema of the face. There was no associated vomiting or wheeze. The angioedema resolved after antihistamine when the mother brought her to the private practitioner.

Mother wondered whether the ingestion of cow milk in the past had caused mild eczema flares and for this reason he was maintained on soy milk. Mother and the family physician concerned about possible contraindication to MMR and influenza vaccine.

In the last few weeks, his eczema has been under good control. He also developed bouts of asthma and mostly were viral induced and was started on inhaled steroid and bronchodilator.

Family history:
Father : current smoker with personal history of childhood asthma in remission
Mother : current allergy to shellfish and personal history of childhood atopic dermatitis in remission
Brother 5: years old - mild episodic asthma

Physical examination:
Weight and height were along the 25th percentile.He looked well apart from patches of eczema distributed over flexural surfaces on both knees, on the nape of the neck and on the face.

Investigations:

RAST(Radioallergosorbent tests)/ Specific IgE KU$_A$/L • Milk1.3, egg 33, peanut, 25
Skin Prick Test (positive result: wheal size > 3mm) • Milk 3mm, egg 7mm, peanut 10mm, soy 2mm, dust mite 3mm
Total IgE 300 (iu/L) (normal < 100)

Provisional diagnosis and problem list:
Atopic child with following clinical allergy:
1) Mild atopic dermatitis
2) Food allergy: IgE mediated (Immediate / hypersensitivity) to egg and peanut. Skin test correlated well with history
3) Sensitisation to cow milk but of doubtful clinical relevance, which will require formal challenge for evaluation.
4) Early onset asthma associated with environmental tobacco exposure and early house dust mite sensitisation

Management:
He continues with soy containing diet. Usual care of atopic dermatitis was advised. He was advised to remain off peanut and egg. Detailed discussion with the parents about strategies to reduce environmental tobacco was made. Household avoidance measures of dust mite should be instituted.

He was given MMR at community care without adverse reaction. He was advised not to be given influenza vaccine in view of his egg allergy.

EpiPen Jr was prescribed together with an action plan in case of anaphylaxis.

Subsequent hospital-based formal challenge of cow's milk at age of 3 found he was tolerant.

Comment:
We are going to review his food allergy problem in 1-2 yearly. 80-90% of children will grow out of egg allergy by age of 8. Peanut allergy is usually persistent. Recent literature reported 10-20% of children may eventually outgrow of the condition. The timing of peanut challenge could be guided by skin test activity or RAST levels. Good asthma control is vital to prevent life threatening food related hypersensitivty.

Prevalence of Food Allergy in Young Children

Food	Young children					Adult
	USA	Australia	France	Norway	China	USA
Milk	2.5%	2.0%	1.1%	3.2%	1.7%	0.3%
Egg	1.3%	3.2%	0.8%	2.0%	3.0%	0.2%
Peanut	0.8%	1.9%	0.7%	-	0.3%	0.6%
Tree Nut	0.2%	0.3%	0.7%	-	-	0.5%
Fish	0.1%	0.07%	-	-	0.3%	0.4%
Shellfish	0.1%	-	1.4%	-	-	2.0%
Overall	6%	-	6%	-	5.2%	3.7%

(Source: Dr. DJ Hill, presented in an invited symposium AAAAI 2006)

Natural History

Most children become tolerant or seem to" outgrow" their food allergies to milk, soy, and egg within a few years. 85% of children with milk allergy become tolerant by age of 3 years.70% of children with egg allergy become tolerant by age of 5 years. Loss of clinical hyperactivity to peanut, though less common, occurs in 20% of peanut allergic children by age of 7 years. Older children and adults with food allergies are less likely to become tolerant. Allergies to other nuts, fish, and shellfish are believed to be more persistent.

Evaluation and Management

In evaluating adverse food reactions, the work-up

depends on the age at onset of the disease (Table 2), on differentiating food intolerance from food hypersensitivity (Table 3), and on differentiating the food hypersensitivity is IgE or non-IgE mediated (Table 4). IgE-mediated allergy typically provokes and on symptoms within minutes to hours. Non-IgE mediated allergy induces symptoms from hours to days. The patient's history not only suggests the type of food hypersensitivity and causative food allergen but also provides information necessary to design an appropriate food challenge for confirming the diagnosis.

Negative prick skin tests is an excellent means of excluding IgE-mediated food allergy.
The majority of children with positive skin tests to foods will not experience allergic symptoms when ingesting that food. The weal size of skin prick and level of food-specific serum IgE help to predict the clinical reactivity upon challenge but not the severity.

Some forms of oral food challenge are necessary to establish the diagnosis of food hypersensitivity. Prescribing a food elimination diet is no different from prescribing any medication and must be based on a firm diagnosis of specific food allergy.

Skin Testing

Skin testing with allergenic extracts is the favoured method of in-vivo testing for IgE-mediated sensitivity. Positive skin test results are useful for demonstrating sensitivity to the patient and the patient's family, and for improving compliance. Skin testing alone is not diagnostic. Skin test results should be correlated with the patient's clinical history. With standardised allergen reagent and technique, the weal sizes of skin prick test correlates with clinical sensitivity but not severity. The larger the skin reaction size, the more likelihood of clinical reaction upon exposure but the size per se could not predict how severe the reaction will be.

Methods of skin testing (Diagram 1)
Percutanous /epicutaneous(prick or puncture),
- Preferred
- Safer
- Easy to perform
- Less painful
- Less sensitive but more specific than intradermal / intracutaneous

Intradermal/intracutaneous testing
- Reserved for weak extracts such as testing for drug allergy.
- When the prick/puncture test is negative to allergens that are strongly suggested by the patient's history or exposure
- Not used in testing food allergens

Patch Test
Takes a few hours to 3 days
To evaluate delay hypersensitivity (e.g., atopic dermatitis due to food, contact dermatitis due to chemicals)

The size of the skin test reactions depends on 1) amount of specific IgE, 2)binding affinity of the IgE antibody, 3)releasability of the patient's mast cell, 4)reactivity of the patients' skin to histamine, 5)area of body used for testing, with the back being more reactive than the arms 6)age (baby younger than 4 months may have false negative results)

Laboratory Test

Allergen-specific IgE antibody
This is the most important analyte measured in the clinical immunology laboratory for diagnosis of allergic disease. It is performed as a confirmatory test to support a clinical history. Quantitative IgE levels to selected foods (milk, egg, fish, and peanut) if above a pre-defined IgE antibody threshold may eliminate the need for food challenges.

Specific in-vitro IgE immunoassays may be preferable to skin testing for patients who :
- Have severe dermatographism, ichthyosis, or generalised eczema
- Use long-acting antihistamines or tricyclic antidepressants
- Are at undue risk if their medications are discontinued
- Refuse skin testing or cannot cooperate with testing
- Have a clinical history suggesting a higher risk of anaphylaxis with skin testing to a particular allergen.

Total serum IgE
This is a diagnostic marker for allergic diseases, but its limitation lies in its wide overlap in the total serum IgE levels between atopic and non-atopic populations such as in parasitic diseases, skin diseases, other than eczema, drug induced conditions, hyper-IgE syndrome, etc.

Mast cell tryptase
This is a marker of mast cell activation during anaphylaxis. Elevated levels, (>10 μg/L) are detectable 1 to 4 hours after the onset of systemic anaphylaxis with hypotension.

Provocation Test

The provocation test or challenge is recognised as the gold standard against all other in-vivo or in-vitro tests. Food challenge is the most common procedure carried out in the paediatric allergy service under the supervision of trained medical personnel. Food challenge procedures should be properly validated and standardised in administration and documentation. This involves giving a child increasing amounts of a food over a period of about several hours and observing for any objective clinical allergic response. This gives parents or families a scientific structure and a plan for the future and the safety of knowing that any reaction will occur within a setting with resuscitative facilities.

Open challenge
Scientifically less vigour
Useful in situation to refute the suspected history where the chance of allergy is low.
Useful for infants and young children in whom subjective symptom is rarely a problem.

Single-Blind Challenge
Very useful in daily clinical allergy practice.
Less time consuming than double-blind-placebo-controlled challenge
Often provides an excellent diagnostic aid in confirming or refuting histories of hypersensitivity reactions, in particular circumstances where patients opinions or concerns may influence the outcome.

Double-Blind-Placebo-Controlled Challenge (Diagram 2)
'Gold standard'
Designed to reproduce the individual's signs and symptoms
Tedious and time-consuming, may take days to complete

Clinical features of food allergy in children (Table 1)

Cutaneous reactions	
IgE mediated	Atopic dermatitis Urticaria Angioedema
Non-IgE Mediated	Contact rash Atopic dermatitis (some forms)
Gastrointestinal reactions	
IgE mediated	Immediate gastrointestinal hypersensitivity (e.g., nausea, vomiting, diarrhoea) Oral allergy syndrome Colic
Non-IgE mediated	Allergic eosinophilic oesophagitis, gastritis, or gastroenteritis Dietary protein colitis, enteropathy
Respiratory reactions	
IgE mediated	Rhinoconjunctivitis Asthma Laryngeal oedema Food-dependent exercise-induced asthma
Non-IgE mediated	Pulmonary haemosiderosis (Heiner's syndrome [rare])
Systemic anaphylaxis	

Age at onset of food allergy (Table 2)

Age (yr)	Food
0-1	Milk, egg
1-2	Fish, peanut
>2	Fruits, vegetables
>3	Pollen-related cross- reactivity (oral allergy syndrome)

Food intolerance: adverse reaction to foods (Table 3)

Toxic/pharmacologic	Nontoxic/intolerance
Bacterial food poisoning	Lactase deficiency
Heavy metal poisoning	Galatosaemia
Scombroid fish poisoning	Pancreatic insufficiency
Caffeine	Hepatobiliary disease
Tyramine	Reflux/hiatal hernia
Histamine	Anorexia nervosa

Food allergy spectrum (Table 4)

IgE-mediated Oral Allergy Syndrome Anaphylaxis Urticaria	→	Non-IgE mediated
	Eosinophilic oesophagitis Eosionphilic gastritis Atopic dermatitis	
		Protein-induced enteritis Protein-induced enteropathy Coeliac disease

Food Allergy in Asia

Food allergy is increasing in prevalence in Western population, but little is known about it in Asia. The perception is that the prevalence in this region is low, but is likely to increase with the global increase in allergy. Asia is unique because of the many different cultures and eating habits, with the resulting occurrence of unique food allergens (Table 5). The lack of availability of epinephrine auto-injectors in many countries is an important issue that needs to be addressed. Large, well designed epidemiological studies are needed so that the scale of the problem can be understood. The labelling of packaged food manufactured in Asia is another area that needs to be improved.

Unique food allergen in Asia (Table 5)

Food	Forms/origin	Reported in Country	Allergen identified	Incidence	Remarks
Birds nest	Chinese delicacy/the saliva of swiftlet	Singapore Hong Kong SAR	A 66 KDa glycoprotein	Most common cause of anaphylaxis in Singaporean children	May outgrow in adulthood
Buckwheat	Noodles, cakes/grain	China Japan Korea	Yes	Ranked fourth in Japan	
Chestnut	Desserts/ tree nut	Korea	At least nine major allergens	Most common food allergen in Korea	Cross react with avocado, peach, apple and mugwort pollen
Chickpea	Staple food/legume	India	Under study	1 in 4 of patients diagnosed of food allergy in India are patients of food allergy	
Royal jelly	Health tonic/ bees	Hong Kong Australia	Under study	Reports of asthma exacerbations	
Sesame	Seasoning/grains	Israel Australia	Under study	Third most common food allergen in Israel	

Food Anaphylaxis

Anaphylaxis is a potentially fatal multi-system syndrome resulting from massive release of inflammatory mediators from mast cells and basophils. Typically, the symptoms can be cutaneous, respiratory, gastrointestinal, and/or cardiovascular. Cutaneous symptoms are the most commonly occurring symptoms in acute anaphylaxis but the absence of cutaneous symptoms does not preclude the diagnosis. These symptoms often have an explosive onset, occurring within seconds to minutes of exposure to the triggering agent, but can also be delayed for several hours after the initial exposure. The acute anaphylactic event can be followed by a late-phase or biphasic reaction occurring 3 to 8 hours after the initial reaction. Biphasic anaphylaxis occurs in 5% to 20% of anaphylactic reactions. Half of fatal anaphylaxis occurs within the first hour.

In our practice, the common triggers are cow milk, egg, fish and peanut. According to Western data, peanut and tree nut are the most common causes of fatal anaphylaxis in children. Idiopathic anaphylaxis is relative uncommon in children. Anaphylactoid (non-IgE-mediated) reaction may occur on the first exposure, whereas IgE-mediated and immunological mediated anaphylactic reactions require sensitisation from a previous exposure unless there is cross-reactivity. Sensitisation is possible through in-utero placental transfer of allergens. This explains why some infants have reaction upon first exposure of foods like cow milk, hen's egg and peanut.

Epinephrine
Epinephrine is universally recommended as the drug of choice in the treatment of acute anaphylaxis and the preferred route of administration in children is intramuscular. Epinephrine is a potent catecholamine with both α-adrenergic and β-adrenergic properties.

The actions of epinephrine reverse all the pathophysiological features of anaphylaxis. Hypotension, peripheral vasodilatation, increased permeability, urticaria, angioedema are all reversed by the α-adrenergic stimulation from epinephrine. The success of cardiopulmonary resuscitation is often dependent upon restoration of aortic diastolic pressure. Increased aortic pressure enhances myocardial perfusion and cerebral perfusion is improved by increased carotid arterial pressure, both of which are results of arterial vasoconstriction and selective redistribution of cardiac output from the α-adrenergic effects of epinephrine. The β-agonist properties of epinephrine have positive inotropic and chronotropic effects on cardiac muscle, cause bronchodilation, and increase the production of intracellular cyclic AMP, thereby inhibiting mast cell mediator release.

The current recommendation of epinephrine dosage is 0.01ml/kg every 10 to 20 minutes up to a maximum of 0.3 to 0.5ml of 1:1000 w/v dilution. Epinephrine is available for out-patient use by parents and patient in a user friendly pre-loaded autoinjector, EpiPen® and EpiPen Jr.® This is a single-use device. EpiPen® dispenses one 0.3mg/dose of 1:1000w/v aqueous epinephrine solution and EpiPenJr® dispenses one 0.15mg /dose. The EpiPen dose is appropriate for a 30kg person, and EpiPen Jr® dose is appropriate for a child 15 kg. The autoinjectors are administered intramuscularly into the vastus lateralis muscle of the thigh. (Diagram 3)

Antihistatmine, systemic corticosteroids, and bronchodilators are secondary medications to be given *after* epinephrine has been administered. Pretreatment with corticosteroids and antihistamines is often ineffective in preventing biphasic anaphylaxis.

Patients with anaphylaxis need a thorough, comprehensive allergy-immunology evaluation to diagnose the specific aetiology. It aims to prevent contact with the allergens that will induce anaphylaxis in susceptible individuals, and to provide strategies for dealing with episodes of allergic anaphylaxis. The physician and family need to implement a written action plan detailing the early recognition of signs and symptoms of anaphylaxis, and the use of an epinephrine auto-injector for self-administration for pre-hospital treatment. Because fatal anaphylaxis occurs despite timely and appropriate treatment, successful avoidance strategies and education remain the mainstay of management.

Frequently asked questions:

What can I do during pregnancy to reduce the chance of my child developing allergies?

- Ensuring the baby's mattress and bedding is free from mite allergen
- Reducing animal allergens
- Reducing dampness in the house
- Developing a smoke-free environment
- Preparing to breast feed
- Does not justify putting pregnant woman on special diet

When is it safe to start to give peanut butter to children?

- for children with atopic parents, it is probably best to avoid it completely before age of 6 months and arguably, the longer you delay the less likely the child is to become allergic to peanut.
- most of the sensitisation of peanut seems occur before age of 2years.

What is the current advice regarding egg allergy and MMR?

- Egg allergy is not a contraindication to MMR (measles, mumps, rubella) vaccination.
- for those children who have experienced a very severe allergic reaction to egg, the vaccination should be given in a hospital setting, where the vaccine can be given by someone trained and equipped to deal with the very small chance of a reaction.
- where the allergy is mild the vaccination may be given in the community.

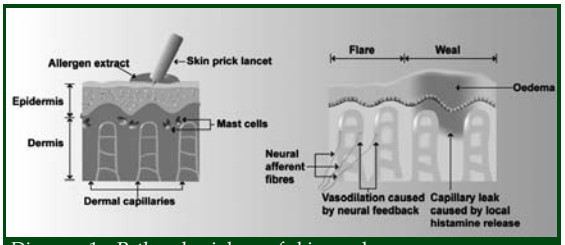

Diagram 1a. Patho-physiology of skin weal response

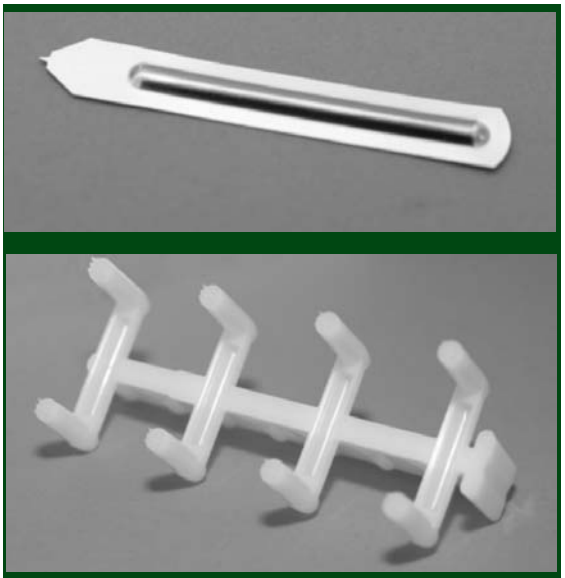
Diagram 1b. Different SPT devices (single head lancet vs. multi-test adaptor)

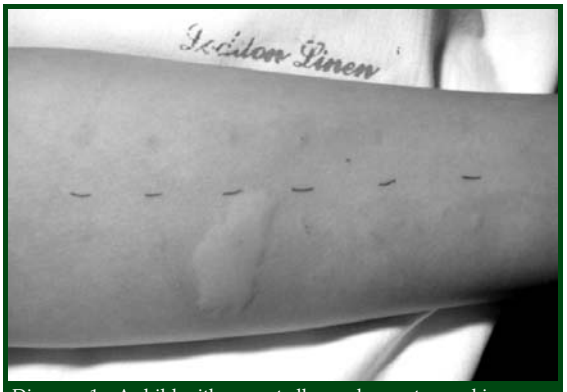
Diagram 1c. A child with peanut allergy shows strong skin reaction to peanut extract

Diagram 2. Picture: One example: use tomato sauce and hamburger to mask the challenge food peanut butter

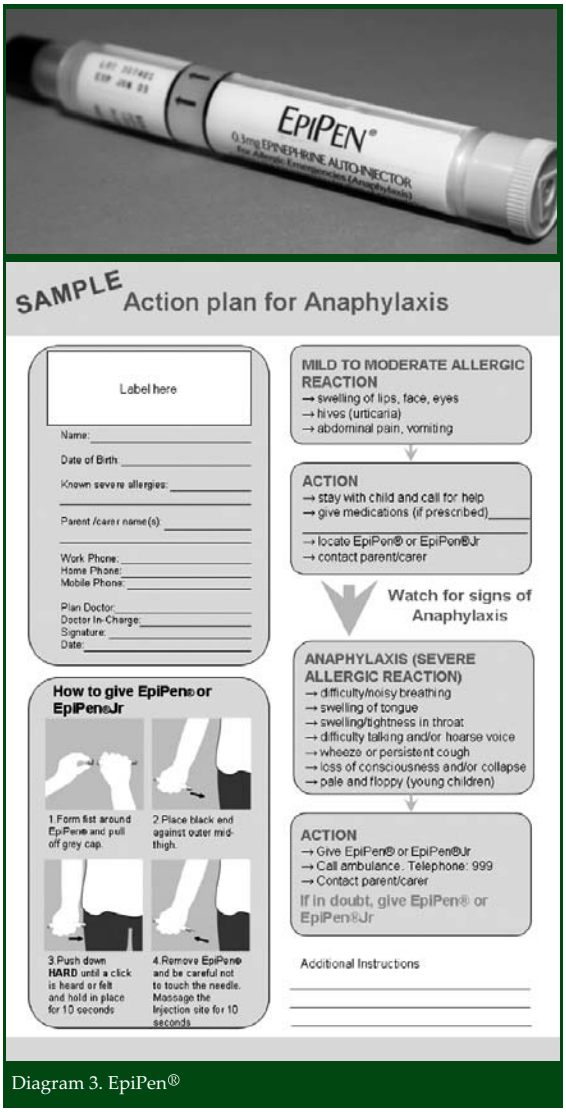

Diagram 3. EpiPen®

Suggested reading:

1. Wood RA. The natural history of food allergy. *Pediatrics*. 2003 111; 1631-7
2. Sampson HA, Mendelson L, Rosen JP.Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992 ;327:380-4
3. American Academy of Allergy, Asthma and Immunology Board of Directors. The use of epinephrine in the treatment of anaphylaxis. *J Allergy Clin Immunol* 1994;94: 666-8.
4. McLean-Tooke AP, Bethune CA, Fay AC, Spickett GP. Adrenaline in the treatment of anaphylaxis: what is the evidence? *BMJ*. 2003;327:1332-5.
5. Australasia Society of Clinical Immunology and Allergy : EpiPen prescription guideline: http://www.allergy.org.au/anaphylaxis/epipen_guidelines.htm
6. Kagan RS, Joseph L, Dufresne C, Gray-Donald K, Turnbull E, Pierre YS, Clarke AE. Prevalence of peanut allergy in primary-school children in Montreal, Canada. *J Allergy Clin Immunol*. 2003;112:1223-8.
7. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110:784-9
8. Simons FE. First-aid treatment of anaphylaxis to food: focus on epinephrine. J Allergy Clin Immunol. 2004;113:837-44.
9. Sampson HA: Food allergy, Part 2: Diagnosis and management. *J Allergy Clin Immunol* 1999;103:981-9
10. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy*. 2005;35:751-6.
11. Shek LP, Lee BW. Food allergy in Asia. *Curr Opin Allergy Clin Immunol* 2006; 6: 197-201

Update on the Management of Infantile Haemangiomas

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2007.

Classification and Clinical Behaviour of Infantile Haemangiomas

Haemangiomas are the most common tumours in the infancy period and affect approximately 10% of infants. However, due to the confusing terminology previously used for various vascular anomalies, inappropriate advice on treatments had often been given to the wrong type of haemangiomas. Mulliken and Glowacki's[1,2] originally proposed a classification of vascular anomalies that divided them into either haemangiomas or vascular malformations. A revised classification was subsequently suggested by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996 by using the same backbone but subdivided these 2 groups of lesions into more refined categories. Among the vascular tumours, it includes infantile haemangiomas, pyogenic granulomas, tufted angiomas, kaposiform haemangioendotheliomas, and spindle-cell haemangioendotheliomas. For vascular malformations, it is classified based on the type of blood vessels involved. For clinical management purpose, it can further be subdivided into low-flow lesions (including port-wine stains, venous malformations, lymphatic malformations, and some combined lesions) and high-flow lesions (including arteriovenous malformations).[3] In order to have a better correlation between the type of haemangiomas and their outcome, the Haemangiomas and Congenital Vascular Malformations Nijmegen working group developed an additional set of diagnostic guidelines.[4] It is based on six distinguishing historical characteristics including: 1) the presence of the anomaly at birth; 2) proliferative rate; 3) evidence of involution; 4) change in volume; 5) pain; and 6) outflow. It also considers 5 physical examination characteristics including: 1) the possibility of emptying or pushing aside the anomaly; 2) changes in volume during engorgement; 3) murmur/'thrill'/pulsation; 4) phleboliths; and 5) hyper- or hypotrophy. These characteristics can assist us in determining the nature of the vascular lesions so we can apply appropriate treatment strategy.

Haemangiomas are caused by inappropriate increase in the proliferation of the vascular cells while vascular malformations are due to inborn errors in vascular morphogenesis. They have distinct clinical behaviour and require different therapeutic approaches. Among vascular tumours, the commonest form in childhood is infantile haemangiomas (also known as capillary haemangiomas, strawberry haemangiomas in the past). Its natural history is well known. It typically emerges after birth and gradually increases in size throughout the subsequent 18 months before starting to regress. The involution process may take several years to complete and often leaves behind a hypopigmented scar. Another problem is that it may induce asymmetry between the involved and normal parts, usually in the form of hypertrophy of the affected region. In the past, active non-intervention remains the mainstay of therapy for most uncomplicated infantile haemangiomas. However, with an improved understanding of the natural course of haemangiomas, more active intervention was adopted in recent years for selected infantile haemangiomas including those found around the "beard areas", periorbital and facial regions.[5]

Infantile haemangiomas located in the head and neck region with a "beard" distribution (including the preauricular areas, chin, anterior neck, and lower lip) are associated with symptomatic obstructive haemangiomas in the upper airway or subglottic areas and some eventually may require tracheotomy. Around 80% of infantile haemagiomas are found in the head and neck region and 8.5% of head and neck infantile haemangiomas have a beard distribution. Those with multiple haemangiomas (i.e. >3 or 4) around the beard areas are particularly at risk. Associated haemangiomas in the upper airway should be monitored closely. [6]

Periorbital infantile haemangiomas including those involving the eyelids may cause amblyopia secondary to occlusion of the pupil. This may eventually lead to anisometropia or strabismus. Those with a size greater than 1 cm in largest diameter are commonly associated with amblyopia and almost 50% of these patients eventually require intervention.[7] Diffuse haemangiomatosis and haemangiomas in patients with PHACES syndrome (**P**osterior fossa malformations, **H**aemangiomas, **A**rterial anomalies, **C**ardiac defects and coarctation of the **A**orta, **E**ye abnormalities, and **S**ternal abnormalities or ventral developmental defects) are also highly associated with visual impairment.[8]

Diffuse haemangiomatosis presenting in neonatal life or early infancy can progress rapidly with a fatal outcome. The affected infants usually have multiple cutaneous haemangiomas as well as deep-seated lesions in different visceral organs such as the liver or sometimes in the central nervous system. Development of hepatomegaly,

high-output cardiac failure, unexplained anaemia or thrombocytopenia in these infants reflects disseminated and aggressive nature of the disease. Early recognition with implementation of effective treatment is essential to improve the chances of survival.[9] Another commonly associated feature of infantile haemangiomas is acquired hypothyroidism. This is secondary to an increase in the type 3 iodothyronine deiodinase secreted by the haemangiomas and is particularly common among infantile hepatic haemangiomas. [10]

Pyogenic granuloma is also known as lobular capillary hemangioma. It is a benign acquired vascular tumour of the skin and mucous membrane and is characterised by an erythematous, dome-shaped papule that bleeds easily. It can be found in the nostrils, oral cavity and the umbilical stump. Majority of the pyogenic granulomas run an uncomplicated course and can be easily treated with localised treatment such as excision or electrocautery. Most will not recur and have good cosmetic results.[11] Other forms of infantile vascular tumours include tufted angiomas and kaposiform haemangioendotheliomas. These vascular tumours are associated with low grade disseminated intravascular coagulopathy clinically manifested as thrombocytopenia with low fibrinogen level (Kasabach Merritt phenomenon). These proliferative vascular tumours are usually associated with hypertrophy of the affected parts of the body or limb. They are now considered as a different disease entity as compared to infantile haemangiomas and have a distinct pattern in their pathogenesis, histology, natural history and response to treatment. They typically respond poorly to systemic corticosteroids and interferon.[12]

Also found in the infancy period is Sturge-Weber syndrome. It is a neurocutaneous syndrome with facial port wine stain (mostly unilateral but can be bilateral). Port wine stain is a form of vascular malformations rather than haemangiomas but patients may also have leptomeningeal angiomatosis and congenital glaucoma. The leptomeningeal angiomatosis is associated with epilepsy in 75-90% of the cases and 60% of them are unfortunately refractory to anticonvulsant treatment. In selected cases, lobectomy with complete excision of the angioma or even hemispherectomy may have to be considered. [13]

Treatment Options of Infantile Haemangiomas

Uncomplicated infantile haemangiomas can be observed for spontaneous involution, especially for those which are small and proliferating slowly in the trunk. However, for those life- or function-threatening, or with the potential of being associated with structural anomalies should be treated as soon as possible.

Corticosteroids can be applied topically, intralesionally or systematically. Topical corticosteroid is effective only for small and superficial lesions. Oral corticosteroid in the form of prednisolone 2 to 3 mg/Kg/day remains to be the commonest form of treatment for infantile haemangiomas. The dose of corticosteroid can be titrated downward clinically according to the response and patients may require a prolonged maintenance phase with a personalised lower dosage over a total duration of 12 to 18 months. We usually attempt to taper the corticosteroids to alternate day low dose and keep it till 12-month of age. Due to the low potency of this approach and high incidence of corticosteroid induced side effects such as stunting growth and obesity in young children, some centres advocated pulse methylprednisolone intravenously 2 mg/kg twice daily for 2 days as an alternative.[14] It has to be followed by a maintenance phase of lower dose oral steroid treatment (2 mg/kg/day) of oral prednisolone. Gradual tapering is recommended. It has been shown that pulse methylprednisolone therapy might result in a more rapid shrinkage of haemangiomas than the usual oral corticosteroid regimen. Periorbital haemangiomas that obstruct the visual axis or exert pressure on the globe is an ocular emergency. Systemic corticosteroids and patching of the unaffected eye should be started early.

Infantile haemangiomas with a deep or subcutaneous component often do not respond to oral steroid or interferon and second line treatment should be considered. For localised haemangiomas with deeper extent, intralesional corticosteroid injection or laser treatment may be the treatment of choice. A variety of different lasers and light sources have been used in the treatment of vascular lesions based on the principle of selective photothermolysis. There are vascular lesions that can easily be treated but some are difficult, the main considerations are the extent and size, anatomical site involved, and the depth of the lesions (i.e. superficial versus subcutaneous).[15] Voluminous haemangiomas (thickness of over 10 mm) can be treated with intralesional laser therapy using the potassium, titanyl, phosphate (KTP) laser, and superficial haemangiomas can be treated with a pulsed dye laser. Fibrosis associated with intralesional therapy can be decreased by injecting small amounts of dilute steroid solution during treatment of the deep haemangiomas.[16] Ulcerated haemangiomas or post-involution sequelae like telangiectasia can also be treated with specific laser. However, the mainstay of therapy for ulcerated haemangiomas remains to be good local wound care, analgesics and treatment of secondary infection.[17]

Interferon alpha (IFN-α) or other agents such as vincristine, thalidomide are therapeutic options for complicated haemangiomas which do not respond to corticosteroids. IFN-αis a cytokine with anti-viral, anti-tumour, and anti-angiogenic properties.[18] IFN-α inhibits the secretion of angiogenic factors such as basic fibroblast growth factor and is an effective treatment modality for high-risk haemangiomas in children, especially those with steroid-resistance. The most commonly used dosage is $3x10^6$units/m^2 IFN-α2b subcutaneously daily for a period of 3 months. According to the response, IFN-α can be tapered to every alternate day or less frequent administration subsequently.[19] However, the most serious complication of this form of treatment is early neurological toxicity in the form of seizure and spastic diplegia, especially among infants.[20, 21]

New drugs such as topical 5% imiquimod cream 3 to 5 times weekly may be helpful in controlling superficial

infantile haemangiomas but has minimal effect on either mixed or deep subcutaneous infantile haemangiomas. Imiquimod induces production of interferon, tumour necrosis factor-α, and antiangiogenesis factors and when applied topically, there is no systemic adverse reaction noted and local irritation with or without crusting are the most common adverse effects. [22]

Patients presenting with Kasabach-Merritt phenomenon have a high morbidity and mortality rate. The majority of them do not respond to corticosteroids and interferon and recently, the use of low dose vincristine ($0.5mg/m^2$) intravenously at weekly interval was shown to be an effective and safe modality. Increase in platelet count and fibrinogen level can usually be achieved within a few weeks. Most patients also showed significant decrease in the size of the vascular lesions but this occurred at a later stage as compared to the recovery of the platelet count and fibrinogen level. The average duration of treatment was around 20 to 30 weeks. Complications included constipation; jaw, bone and abdominal pain; loss of deep tendon reflexes or even foot drop. Regular monitoring of the emergence of peripheral neuropathy by nerve conduction study is mandatory. Most of the neuropathies are transient in character and will resolve spontaneously upon stopping of the vincristine. Another potential risk of this form of treatment is the skin burn induced by extravasations of the vincristine. Therefore this form of treatment should be given in specialty centres and sometimes the use of central venous catheter is recommended due to the difficult venous access. We had treated 3 patients with Kasabach-Merritt phenomenon who were refractory to corticosteroids and interferon treatment and 2/3 patients responded with no significant complications. The only one who failed to respond had kaposiform lymphoendothelioma by biopsy. Whether the difference in histology may account for the suboptimal response remains to be proven. [12]

Conclusion

Vascular tumours are commonly found in infants and young children and they have marked heterogeneity in terms of their clinical behaviour and response to treatment. If not managed optimally and early, disfiguring or dysfunctioning long term complications may occur in some patients. In severe cases such as haemangiomas of the upper airway or disseminated haemangiomatosis, it may even lead to fatal outcome. When we encounter an infant with haemangiomas, active non-intervention should be applied with caution and corticosteroids may not be the best initial option always. For complicated cases, early referral to specialty units can help to minimise unnecessary delay or treatment complications.

References

1. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. *J Pediatr Surg* 1983;18(6):894-900.
2. Mulliken JB, Glowacki J. Classification of pediatric vascular lesions. *Plast Reconstr Surg* 1982;70(1):120-1.
3. Wassef M, Vanwijck R, Clapuyt P, Boon L, Magalon G. [Vascular tumours and malformations, classification, pathology and imaging]. *Ann Chir Plast Esthet* 2006;51(4-5):263-81.
4. Zweep HP, Rieu PN, van Die CE, Boll AP, Steijlen PM, Spauwen PH. [Haemangiomas and congenital vascular malformations: their classification and diagnosis]. *Ned Tijdschr Geneeskd* 2002;146(23):1072-7.
5. Batniji RK, Buckingham ED, Williams EF, 3rd. An aesthetic approach to facial hemangiomas. *Arch Facial Plast Surg* 2005;7(5):301-6.
6. Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a "beard" distribution. *J Pediatr* 1997;131(4):643-6.
7. Schwartz SR, Blei F, Ceisler E, Steele M, Furlan L, Kodsi S. Risk factors for amblyopia in children with capillary hemangiomas of the eyelids and orbit. *J Aapos* 2006;10(3):262-8.
8. Kronenberg A, Blei F, Ceisler E, Steele M, Furlan L, Kodsi S. Ocular and systemic manifestations of PHACES (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects and coarctation of the Aorta, Eye abnormalities, and Sternal abnormalities or ventral developmental defects) syndrome. *J Aapos* 2005;9(2):169-73.
9. Byard RW, Burrows PE, Izakawa T, Silver MM. Diffuse infantile haemangiomatosis: clinicopathological features and management problems in five fatal cases. *Eur J Pediatr* 1991;150(4):224-7.
10. Ho J, Kendrick V, Dewey D, Pacaud D. New insight into the pathophysiology of severe hypothyroidism in an infant with multiple hepatic hemangiomas. *J Pediatr Endocrinol Metab* 2005;18(5):511-4.
11. Pagliai KA, Cohen BA. Pyogenic granuloma in children. *Pediatr Dermatol* 2004;21(1):10-3.
12. Haisley-Royster C, Enjolras O, Frieden IJ, et al. Kasabach-merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* 2002;24(6):459-62.
13. Di Rocco C, Tamburrini G. Sturge-Weber syndrome. *Childs Nerv Syst* 2006;22(8):909-21.
14. Delesalle F, Staumont D, Houmany MA, Breviere GM, Piette F. Pulse methylprednisolone therapy for threatening periocular haemangiomas of infancy. *Acta Derm Venereol* 2006;86(5):429-32.
15. Astner S, Anderson RR. Treating vascular lesions. *Dermatol Ther* 2005;18(3):267-81.
16. Burstein FD, Williams JK, Schwentker AR, Nahai F. Intralesional laser therapy treatment for hemangiomas: technical evolution. *J Craniofac Surg* 2006;17(4):756-60.
17. Chan YC, Giam YC. Guidelines of care for cutaneous haemangiomas. *Ann Acad Med Singapore* 2005;34(1):117-23.
18. Lindner DJ. Interferons as antiangiogenic agents. *Curr Oncol Rep* 2002;4(6):510-4.
19. Hastings MM, Milot J, Barsoum-Homsy M, Hershon L, Dubois J, Leclerc JM. Recombinant interferon alfa-2b in the treatment of vision-threatening capillary hemangiomas in childhood. *J Aapos* 1997;1(4):226-30.
20. Worle H, Maass E, Kohler B, Treuner J. Interferon alpha-2a therapy in haemangiomas of infancy: spastic diplegia as a severe complication. *Eur J Pediatr* 1999;158(4):344.
21. Ameen M, Russell-Jones R. Seizures associated with interferon-alpha treatment of cutaneous malignancies. *Br J Dermatol* 1999;141(2):386-7.
22. Ho NT, Lansang P, Pope E. Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. *J Am Acad Dermatol* 2007;56(1):63-8.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Update on the Management of Infantile Haemangiomas" by Dr. Godfrey CF Chan, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2007. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. The revised classification by the International Society for the Study of Vascular Anomalies (ISSVA) includes the following as vascular tumours, except:
a. pyogenic granulomas
b. tufted angiomas
c. angiofibroma
d. infantile haemangiomas
e. kaposiform haemangioendotheliomas

2. The revised classification by the International Society for the Study of Vascular Anomalies (ISSVA) includes the following as vascular malformations, except:
a. aortic aneurysm
b. port-wine stains
c. venous malformations
d. lymphatic malformations
e. arteriovenous malformations

3. The additional set of diagnostic guidelines by the Haemangiomas and Congenital Vascular Malformations Nijmegen working group includes the followings, except:
a. the presence of the anomaly at birth
b. proliferative rate
c. evidence of inflammation
d. change in volume
e. pain

4. Infantile haemangiomas (capillary haemangiomas) can undergo involution spontaneously but in which of the following location, early treatment or intervention is currently recommended:
a. haemangioma around the periorbital area
b. haemangioma around the periumbilical area
c. haemangioma around the perineal area
d. haemangioma around the waist area
e. haemangioma around the neck area

5. Since infantile haemangiomas (capillary haemangiomas) may have the following potential adverse outcome(s), intervention is advisable if it is located in the facial region: (choose the best answer)
a. may take a long time to involute
b. often leaves behind a hypopigmented scar
c. may induce asymmetry
d. untoward psychological effect on the child
e. all of the above

6. Infantile haemangiomas located in the "beard" areas are associated with symptomatic obstructive haemangiomas in the upper airway and some eventually may require tracheotomy. The "beard" areas include the followings, except:
a. preauricular areas
b. chin
c. anterior neck
d. upper lip
e. lower lip

7. Which of the following statements about infantile haemangiomas is correct:
a. 50% of infantile haemagiomas are found in the head and neck region
b. 85% of head and neck infantile haemangiomas have a beard distribution
c. haemangiomas affect approximately 20% of infants
d. periorbital haemangiomas >1 cm diameter are commonly associated with amblyopia
e. multiple haemangiomas (i.e. >3 or 4) around the periorbital areas are at risk of having concomitant haemangiomas in the upper airway

8. Corticosteroids remain to be the commonest form of treatment for infantile haemangiomas. Which of the following statements about steroid treatment is correct :
a. standard dose of oral corticosteroid (2mg/Kg/day) should be applied for at least 6 to 12 months
b. the maximum duration of oral steroid therapy is 12 months
c. pulse methylprednisolone regimen can replace the maintenance oral steroid
d. topical corticosteroid is as effective as oral steroid
e. haemangiomas with a deep or subcutaneous component often do not respond to oral steroid

9. The most threatening complication of interferon alpha (IFN-) treatment in infancy period is:
a. neurological toxicity
b. hypothyroidism
c. neutropenia
d. anaphylaxis
e. none of the above

10. The current recommended treatment for Kasabach-Merritt phenomenon is:
a. low dose vincristine
b. pulse methylprednisolone
c. interferon alpha
d. thalidomide
e. no effective treatment

ANSWER SHEET FOR MARCH 2007

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2007 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Update on the Management of Infantile Haemangiomas

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Answers to February 2007 issue

Hypertension 2007' - Update on How to Choose and Prescribe the Best Medications for our Patients

1. T 2. T 3. T 4. T 5. T 6. F 7. F 8. F 9. F 10. F

Management of Atopic Eczema in Children

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Introduction

Atopy is used to describe a form of hypersensitivity based on a hereditary influence. This term was originated by Coca and Cooke in 1923[1,2]. Currently, it is confined to be used in those patients who suffer from excessive IgE response with low dose allergen. Eczema means chronic fluctuating skin eruption. Acute form of eruption presents with itching, redness, papules, vesicles, edema, serous discharge and crusts. The diagnostic criteria of atopic eczema were agreed by the Academy of dermatology at 59th annual meeting in 2001. In diagnosing atopic eczema, 3 major and 3 minor criteria are required. The following table shows the major and minor diagnostic criteria:-

Major	
Pruritus	Chronic or relapsing dermatitis
Lesions of typical morphology	Personal or familial history of atopy
Lesions of typical distribution for age	
Minor	
Early onset	Environmental factors as triggers
Ichthyosis Vulgaris	Emotional factors as triggers
Palmar hyperlinearity	White dermographism
Keratosis Pilaris	- lesional
Xerosis	- non-lesional
Hand eczema	Delayed blanching
Cheilitis	Keratoconus
Conjunctivitis	Anterior sub-capsular cataracts
Dennie-Morgan infraorbital fold	Positive on Prick test
Orbital darkening	Increase serum IgE
Facial pallor	Increase in skin infections
Facial erythema	Impaired CMI
Pityriasis Alba	Hanifin & Rajka (modified)
Neck folds	Infra auricular fissures
Itch increases when sweating	Angular cheilitis
Wool intolerance	Digital pulpitis
Solvents intolerance	Juvenile plantar dermatitis
Follicular accentuation	Scalp scaling
Skin reaction to food	Scalp dermatitis
-Ingested	Head lamp sign
-By contact	Eosinophilia
	Selected hematologic
	- abnormalities
	- Additional

Epidemiology and Prevalence:

In 1999, Williams et al conducted a large scale cross-sectional study in 56 countries.[3] It was a questionnaire survey of school children aged 6-7 years and 13-14 years. The diagnostic criteria were the presence of itchiness and relapsing rash in past 12 months and it mainly affected skin creases. The severity was assessed by at least 1 night or more sleep disturbance in a week. The prevalence rate among different countries ranged from less than 2% to greater than 16%. The prevalence rate of eczema was 3.9 - 27.2% in Hong Kong. Japan and Sweden appeared as the highest. The overall male to female ratio was 1:1.3.

Another long term cohort study was conducted by Williams et al in 1998.[4] There were 6877 babies born on 3-9 March 1958. They were then followed up at the ages of 7 years, 11 years, 16 years and 23 years. It was found that overall 15% of UK population suffered from atopic eczema at the age of 23 years. There were 571 studied children out of the 6877 developed eczema at 7 years of age. Of these 571 patients, 65% showed clear up of the disease at 11 years old, 74% showed clear up of the eczema at 16 years of age. A quarter of the 571 patients had persistent disease by age of 23 years.

In Queen Mary Hospital, the paediatric dermatology clinic started in June 2000. There are 767 paediatric patients in total actively followed up in a 6 years interval. Forty seven% (365/767) of our workload spent on the atopic eczema. There are a few refractory cases required second line systemic immunosuppressant.

Pathogenesis:

Many features of atopic dermatitis reflect a cell mediated or delayed hypersensitivity. Pathology and immunology studies on the affected skin showed that the epidermal dendritic cells carry all the IgE receptors including high affinity Fc receptors for IgE I (FcER I). In acute flare ups of atopic eczema, higher levels of FcER I were detected.[5,6] The relevant IgE binds to low dose external allergens. When IgE binds with allergens to form a complex, it will activate the antigen presenting cells in particularly dendritic cells. The dendritic cells then move and activate the lymphocyte in the regional lymph nodes. Dendritic cell preferentially induces Type 2 T-helper cell (Th2, CD4+) response and subsequently induces cytokines IL-3,-4,-5 release that favour IgE synthesis, mast cell activation and eosinophilia.[7,8] The imbalance between the type 1 and type 2 T-helper lymphocytes with polarisation towards the type 2 T-helper activity had consistently been found in atopy.

Treatment

The most important goal of the treatment is to break the vicious circle (allergen, skin breakage, itchiness and scratch). Initiation of aggressive management is

necessary to induce remission of disease activity then step down for maintenance therapy.

Avoidance of irritants and allergens is the first step. Allergens like sodium lauryl sulfate which dissolves the natural skin barrier can exacerbate the atopic eczema.[9] Solvents like alcohol, gasoline and kerosene should be avoided. Detail history is needed to identify any topical, respiratory and dietary allergen. Once the suspected culprit has been identified, confirmatory allergic tests should be arranged. Avoidance and elimination diet should be implemented once the culprit is confirmed.

Other behavioural measures like exclusive breast milk was studied in the past for reducing atopic eczema.[10] A meta-anaylsis in Cochrane library showed breast feeding or prolong use of hydrolysed formula has protective effects on allergy including atopic eczema compared with cow's milk feeding.[11] Usage of probiotics in preventing early atopy in high risk children is still controversial. Some of the European studies showed that transferring the patient to high altitudes will result in less atopy or less severe form of the disease. This observation suggested that change in weather may precipitate the atopy. Parents should pay more attention in treating the disease flare ups when there is a significant weather change.

There are different modalities of medical therapy for inducing remissions of atopic eczema which include topical agents, phototherapy and systemic medications. Topical agents are further divided into moisturisers, topical steroids and topical immunomodulators. Topical moisturisers is an important general measure to prevent skin breakage and itchiness.[12] Topical moisturisers should be applied soon after soaking or bathing, they help in trapping water in the stratum corneum temporarily. Maintenance of the desired pliability of the skin and decreasing trans-epidermal water loss (TEWL) are the main aim of the moisturiser therapy. Many types of moisturisers are available in town, they are: 1) products of petrolatum; 2) Newer products containing ceramides/cholesterol and fatty acids which correct the TEWL for up to 24 hours. However, some of the moisturisers may trap/contain irritants. Newer formulations contain dimethicone with aluminum magnesium hydroxide stearate which effectively protect the underlying skin. Topical agents like calamine lotion, menthol/phenol in aqueous cream and crotamiton may be used but generally without significant clinical response.

Topical steroids have been used for many decades.[13] In Hong Kong, parents generally refuse or afraid of using "steroid"-steroid phobia. Parents are usually afraid of the side effects of steroids. The side effects of topical steroids can be divided into two categories, namely systemic and local side effects. Systemic side effects are as follows: hyperglycaemia, hypertension, cataract, short stature, Cushing syndrome, osteoporosis, suppression of hypothalamic pituitary axis (HPA). Topical side effects include skin atrophy, skin infection, striae and telangiectasia.

Targeted use of different types and forms of topical steroid is the crucial element in reducing the occurrence of the side effects. No long term usage of topical steroid is advised. Use topical steroids when necessary and stop the medication in 1-2 days once the rash disappears. Start with less potent steroids first and step up the strength if the condition does not improve. Avoid using moderate potent steroids over the face and perineal regions in children. Most potent topical steroids are generally forbidden to be used in childhood eczema. Simple classification of the topical steroids is listed as below:

- Less potent steroids
  - Hydrocortione
- Moderate potent steroids
  - Mometasone (Elomet)
  - Betamethasone (Diprosone)
- Most potent steroid
  - Clobetasol (Dermovate)

Besides potency, the bioavailability of topical steroids also depends on the vehicle, duration of therapy and method of therapy. For example, cream and gel forms have less systemic absorption than ointment. Occlusive methods on the other hand, will have more systemic effect when compared with non-occlusive ones.[14] Duration of the occlusive will also significantly affect the bioavailability. Long duration of more than 96 hours will sharply increase the systemic absorption. Finally the integrity of the skin and area of steroid application are important for the drug penetration and systemic side effects.

A few studies showed that occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration. However occlusive dressing >96 hours markedly enhances penetration. Mometasone ointment penetration is around 2 times better then mometasone cream.[15] Sixteen% of 97 paediatric patients developed HPA suppression after 3 weeks daily topical mometasone therapy over a mean basal surface area of 41% (ranging from 15-94%).

To reduce the side effects, a new group of topical agents was developed in the past decade i.e. topical immune modulator (TIM). Two different drugs have been launched on the market and they are named Tacrolimus and Pimecrolimus.

Tacrolimus is a macrolide immunosuppressant previously known by its experimental name FK506. It was first discovered in 1984 by Fujisawa. The chemical was produced by Streptomyces tsukabaenis (Fungus found in the soil near Tsububa in Japan. The name of this chemical was called tacrolimus because: T from Tsububa, -acroli from Macrolide, -mu from immune, -s from suppressant. It acts as a topical inhibitor of the phosphatase calcineurin. Because of the large molecular size, it is less able to penetrate thick skin compared with steroids. The advantage of this TIM is that it does not cause skin atrophy. There were ten different studies performed from 1994-2001.[16, 17] Five out of 10 randomised control trials showed 70-80% improvement in studies patients compared with 10-20% in placebo. Adverse effects of the Tacrolimus are mainly related to its systemic absorption. Minimal systemic absorption is expected when its use is within 3 weeks to 3 months. 76% of patients showed blood level <1ng/ml of tacrolimus when given for 1year. In the ten studies, only 2 patients had 20ng/ml of tacrolimus in the blood, which correlated with the severity of the disease.The common side effects and the

percentage of occurrence of the topical tacrolimus are as follows: burning sensation 46-58%, Flu like symptoms 20-30%, headache 20%. Other rarer adverse effects include tingling sensation, alcohol intolerance, acne and folliculitis. The potency of the tacrolimus is comparable to moderate potent steroid (betamethasone).

Another TIM is named pimecrolimus (formerly SDZ ASM 981).[18] Totally more than 400 ascomycin derivatives had been synthesised and finally SDZ ASM 981 was chosen for development because of its favourable safety profile and cutaneous efficacy. It was derived from a fungus, Streptomyces hygroscopicus var. ascomyceticus. The chemical structure is similar to Tacrolimus. In contrast to Tacrolimus, oral Pimecrolimus is a poor systemic immune suppressant, reducing the likelihood of systemic toxicity. The measured blood concentrations of Pimecrolimus were consistently low in both adult and paediatric patient as young as 3 months of age. (99% had <2ng/ml regardless of age, extent of BSA treated, duration of therapy). Therefore it is safe to use the Pimecrolimus in 3 month old babies, whilst Tacrolimus is advised to be used in children older than 3 years.

Oral antipruritics are commonly prescribed to the patients who suffer from atopic eczema, and antihistamine is the drug of choice.[19] Sedative antihistamines like promethazine (phenergen), diphenhydramine (benadryl), chlorpheniramine (piriton), dexchlorpheniramine (polaramine) and hydroxyzine (atarax) are usually used. Non-sedative antihistamines include loratadine (clarityne) and cetirizine (zyrtec).

Alternate therapy may be considered for severe refractory atopic eczema. Narrow band UVB, cyclosporin A[20] and azathioprine[21] had been shown to be effective ways in treating severe cases. In severe atopic eczema, patients may also suffer from complications like eczema herpeticum, low self esteem and even major depression. In Queen Mary Hospital we have started 6 patients on low dose azathioprine with reasonable effects.

Conclusion

Atopic eczema is the commonest paediatric dermatologic problem. In acute flare ups of the disease, aggressive topical treatment with either steroid or topical immuno-modulator should be offered to induce complete remission. Subsequent management requires emollient to reduce the trans-epidermal water loss. Sometimes, anti-histamines can be added in order to break the itchy-scratch-inflammation vicious circle. When choosing topical steroid therapy, one should avoid the prolonged use of medication for >three weeks. Use of the most potent steroid in childhood eczema should be avoided since it associates with higher chance of both systemic and local side effects. Newer topical immuno-modulator is a drug of choice for their steroid sparing effect. In severe refractory cases, patients should be referred to tertiary centres for second line systemic immuno-suppressants.

References

1. Cohen S, Dworetzky M, Frick OL. Coca and Cooke on the classification of hypersensitiveness. *J Allergy Clin Immunol* 2003;111(1):205-10.
2. Coca AF, RA C. On the classification of the phenomenon of hypersensitiveness J Immunol 1923;8:163-82.
3. Williams H, Robertson C, Stewart A, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103(1 Pt 1):125-38.
4. Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. *Br J Dermatol* 1998;139(5):834-9.
5. Kimata H, Saxon A. Subset of natural killer cells is induced by immune complexes to display Fc receptors for IgE and IgA and demonstrates isotype regulatory function. *J Clin Invest* 1988;82(1):160-7.
6. Holter W. Regulation of interleukin 4 production and of interleukin 4-producing cells. *Int Arch Allergy Immunol* 1992;98(4):273-8.
7. Nicolas JF, Rozieres A, Castelain M. [Pathogenesis of atopic dermatitis]. *Ann Dermatol Venereol* 2005;132 Spec No 1:1S44-52.
8. Miraglia del Giudice M, Decimo F, Leonardi S, et al. Immune dysregulation in atopic dermatitis. *Allergy Asthma Proc* 2006;27(6):451-5.
9. Loffler H, Steffes A, Happle R, Effendy I. Allergy and irritation: an adverse association in patients with atopic eczema. *Acta Derm Venereol* 2003;83(5):328-31.
10. Kramer MS, Kakuma R. The optimal duration of exclusive breastfeeding: a systematic review. *Adv Exp Med Biol* 2004;554:63-77.
11. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006(4):CD003741.
12. Lazar AP, Lazar P. Dry skin, water, and lubrication. *Dermatol Clin* 1991;9(1):45-51.
13. Goustas P, Cork MJ, Higson D. Eumovate (clobetasone butyrate 0.05%) cream: a review of clinical efficacy and safety. *J Dermatolog Treat* 2003;14(2):71-85.
14. Oranje AP, Devillers AC, Kunz B, et al. Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. *J Eur Acad Dermatol Venereol* 2006;20(10):1277-86.
15. Prakash A, Benfield P. Topical mometasone. A review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. *Drugs* 1998;55(1):145-63.
16. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol* 2001;44(1 Suppl):S28-38.
17. Bigby M. A thorough systematic review of treatments for atopic eczema. Arch Dermatol 2001;137(12):1635-6.
18. Wahn U, Bos JD, Goodfield M, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics 2002;110(1 Pt 1):e2.
19. Greaves MW. Antihistamines in dermatology. *Skin Pharmacol Physiol* 2005;18(5):220-9.
20. Lee SS, Tan AW, Giam YC. Cyclosporin in the treatment of severe atopic dermatitis: a retrospective study. *Ann Acad Med Singapore* 2004;33(3):311-3.
21. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006;367(9513):839-46.

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Can Allergies Be Cured?

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What are allergies?

Allergies are caused by immune-mediated reactions to seemingly innocuous substances such as pollens, foods and cosmetics. It has been estimated that 25% of Hong Kong children suffer from allergic rhinitis, 12% from asthma, 6% from eczema and 5% from food allergies[1]. Although these diseases are rarely fatal, they can significantly affect the quality of life. For example, allergic rhinitis has been linked to sleep apnoea and hyperactivity in children[2]. Complications such as chronic sinus infection, glue ears, dental abnormalities and corneal abrasions can arise in severe cases. Young children with allergic rhinitis have up to a 30% chance of eventually developing asthma.

Can allergies be prevented?

Family history is very useful in predicting how likely a child will develop allergies. Someone whose parents are allergic has a greater than 60% chance of developing allergies. However, there are ways to reduce this risk. Studies have shown that infants who were exclusively breastfed for at least 6 months have a much lower risk of developing significant allergies[3]. Other studies showed that lowering house dust mite allergen levels in an infant's environment reduces the risk of mite allergy and asthma[4]. Interestingly, recent data suggest that children who have been living with cats since birth are half as likely to develop cat allergy as someone who did not grow up with cats[5]. It seems that certain allergens such as cat dander induce tolerance in the immune system when exposed at high doses early in life, whereas other allergens such as pollens and house dust mites induce sensitisation. Effective house dust mite avoidance measures include the removal of carpets, the use of special mite-proof covers for the beddings, and keeping the relative humidity constantly below 55%.

Can allergies be cured?

Although some people can outgrow food allergy, allergy to inhalants tends to be lifelong. It is important to find out what the offending allergens are, since the first line of treatment is to remove those allergens from the environment. This means avoiding allergic foods, furry pets, and instituting mite control. Diagnosing allergies by skin prick tests is safe and accurate, and can give an answer within 15 minutes. However, some allergens such as pollens, cats and mites can be difficult or impossible to eliminate. Studies have shown significant levels of cat allergens in public places such as schools and libraries[6]. Medications such as antihistamines and nasal steroid sprays can reduce symptoms, but many patients do not like using medicines continuously for an indefinite period of time. Allergen desensitization treatment, also called allergen immunotherapy or allergy vaccines, can often help people with severe symptoms uncontrolled by allergen avoidance and medications. This technique was invented in 1911[7], but advanced biotechnologies now available have greatly improved its safety and efficacy. It is widely used in Europe and the US to treat nasal and ocular allergy, asthma and certain types of skin allergy. Vaccines to treat peanut allergy are under development and will hopefully become available within a few years. During the initial phase of treatment, the dose of vaccine is increased gradually through a series of injections until the therapeutic dose is reached. This dose is then given periodically, usually every month. This builds up an immune tolerance, and the person gradually loses sensitivity towards these allergens. Clinical improvement is usually seen within 3 to 6 months, by which time the majority of patients can stop using medications. Some patients even readopt their pets from relatives and friends. Treatment should continue for three to five years, after which the improvement appears to be long lasting. Although it is too early to say whether these patients are cured, but studies of patients who underwent two years of treatment showed no loss of efficacy six years after treatment has ceased[8]. Moreover, the result of a large European study showed that children who have been desensitised to pollens were 2.6-fold less likely to develop asthma than children who received placebo injections[9]. These children were also less likely to develop sensitivities to other allergens. This is very encouraging news indeed, as this is the first time a treatment is shown to prevent asthma and allergy. Studies using other routes of administration such as sublingual tablets are being carried out to find more convenient alternatives.

Patients with food allergies can develop symptoms ranging from mild itching to full blown anaphylaxis. Food allergies can cause significant difficulties in daily lives, especially for caregivers of young children with severe symptoms. Living with the fear that the next bite of food can lead to serious consequences can take a

major toll psychologically. There have been anecdotal reports of successful oral desensitisation of immediate type food allergies such as milk, egg and shellfish. A recent study of oral egg desensitisation in seven children with non-anaphylactic allergic reactions to egg showed that five subjects could be desensitised to tolerate at least 8 g of egg without reaction[10]. This procedure must be carried out under strict medical supervision, but the development of modified food allergens with reduced allergenicity in the future holds promise as a cure for food allergies.

References

1. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). *Pediatr Allergy Immunol*. 2004;15(1):72-8.
2. Xu Z, Cheuk DK, Lee SL.Clinical evaluation in predicting childhood obstructive sleep apnea. *Chest*. 2006 Dec;130(6):1765-71.
3. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet*. 1995;346(8982):1065-9.
4. Marks GB, Mihrshahi S, Kemp AS, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol*. 2006 Jul;118(1):53-61.
5. Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. *Am J Respir Crit Care Med*. 2002;166(5):696-702.
6. Tranter DC. Indoor allergens in settled school dust: a review of findings and significant factors. *Clin Exp Allergy*. 2005;35(2):126-36.
7. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572-1574.
8. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. *J Allergy Clin Immunol*. 1993;91:709-722.
9. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, Koivikko A, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109:251-256.
10. Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol*. 2007;119(1):199-205.

Application of Echocardiography in Clinic Practice

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Echocardiogram is a totally non-invasive ultrasound assessment of the heart and the big vessels. It differs from ordinary ultrasound scan by providing information on
1. function, both dynamic systolic and diastolic
2. haemodynamics
3. anatomy
of the heart and related big vessels.

Echocardiogram can be performed under resting condition as baseline comprehensive assessment, or under controlled stress condition for functional assessment of significance of valvular lesion or inducible ischaemia in coronary artery disease.

In this short article, we shall discuss some of the applications of echocardiography in common problems in clinic practice.

A. Assessment of chest pain symptom

Symptom of chest pain is a common presenting symptom in clinics. The list of possible causes from any medical textbook includes[1]
a. coronary artery disease
b. aortic dissection
c. pulmonary embolism
d. peptic ulcer disease
e. reflux oesophagitis
f. musculoskeletal pain
g. pleuritis / pericarditis
h. neuritis
i. gall stone
j. psychosomatic etc

Most of the time clinicians want to rule out coronary artery disease and aortic dissection etc as they are treatable and carry most of the prognosis. A comprehensive echocardiogram can give us clues and even make the diagnosis of acute coronary syndrome, aortic dissection or pulmonary embolism. (Fig. 1)

Regional wall motion abnormality and thinning indicates old myocardial infarction or significant ischaemia at rest. Although Treadmill ECG is usually ordered to look for possible ischaemia, an exercise stress echocardiogram is usually more helpful and accurate in diagnosis and risk stratification.

Traditional Treadmill ECG uses ST segment changes as an indicator of underlying myocardial ischaemia. However Treadmill ECG has limited sensitivity in pre-menopausal women because of their lower prevalence of coronary artery disease[2]. Moreover, common baseline ECG abnormalities like bundle branch block, left ventricular hypertrophy, digoxin or simple non-specific ST segment or T wave abnormality can make subsequent ECG changes non-specific to ischaemia and the whole test inconclusive[2].

Exercise stress echocardiogram uses direct visualisation of the LV wall motion as a marker of inducible ischaemia. Wall motion abnormality occurs earlier in the ischaemic cascade and this makes the test more sensitive and specific (overall sensitivity 85%, specificity 80%) and equivalent to nuclear myocardial perfusion scan[3,4] (Fig. 2). The advantages of exercise stress echocardiogram are cost-efficient, no need of contrast or radiation exposure and high acceptability to the patient. The patient can be informed of the result right after the test in the clinic. Apart from diagnosis, it stratifies patients into different risk categories and prognosticates[5] (Fig. 3).

B. Assessment of exertional shortness of breath or decrease in exercise tolerance

Exertional shortness of breath or subjective decrease in exercise tolerance is another common presenting symptom in clinical practice. The causes can be divided into three categories (1):
a. cardiac causes like systolic or diastolic heart failure
b.pulmonary causes like COAD, fibosis, pleural effusion etc
c. systemic causes like anaemia, thyrotoxicosis etc
A detailed history and examination can rule out most of the systemic and pulmonary causes. A comprehensive echocardiogram is indispensable in the diagnosis of cardiac causes of exertional shortness of breath.
Most practitioners focus only on the ejection fraction (EF) of the Echocardiogram report. A low EF suggests systolic heart failure is a possible cause for the patient's symptom. However , more than 40% of patients suffer from diastolic heart failure with normal ejection fraction > 50%[6,7]. (Fig. 4)
Diastolic heart failure means the heart needs to be filled with increased pressure (elevated LV end-diastolic pressure). In the old days, diagnosis can only be arrived at by invasive cardiac catheterisation[8]. However, nowadays non-invasive echocardiographic assessment has been considered the choice and tool in diastolic cardiac assessment for clinical studies and cardiology practice.
I do not intend to discuss cardiac diastology in this short article as it is more complex than simple systolic ejection fraction. Patients with systolic heart failure

usually complain with fatigue due to inadequate cardiac output. On the other hand, patient with diastolic heart failure has dominant "congestive" symptom either shortness of breath, orthopnoea or ankle oedema.

LV diastolic dysfunction can be classified into stages (Fig. 5)
a. Stage 1 : impaired LV relaxation, a stage with minimal symptom at rest but disproportional shortness of breath due to elevated filling pressure when tachycardia sets in during exertional or atrial fibrillation
b. Stage 2 : pseudo-normalisation, a stage with exertional SOB on minimal exertion due to elevated filling pressure at rest
c. Stage 3 and stage 4 : reversible and irreversible restrictive , the advanced stages of diastolic dysfunction with severe symptoms even at rest and poor prognosis.

Diastolic heart failure is indeed common and an usually missed diagnosis. Hypertension and coronary artery disease are two common causes of LV diastolic dysfunction. Hypertension causing left ventricular hypertrophy is the commonest cause of increased LV stiffness thus impaired relaxation.
By applying Doppler study on trans-mitral inflow, pulmonary venous inflow and Spectral Tissue Doppler (TDI) on mitral annular velocity, previously complex diastolic parameters can easily and quickly be elucidated[9,10]. Practitioners do not need to memorise all these terminology but it is the duty of the reporting cardiologist to comment on the ventricular diastolic function and evidence of elevated filling pressure in a comprehensive echocardiogram. (Fig. 4)
Treatment of diastolic dysfunction needs to be individualised and will not be discussed here.

C. Incidental findings of heart murmur, abnormal ECG or cardiomegaly on CXR

An incidental finding of possible cardiac abnormality is a common result of cardiac consultation.

1. Heart murmurs can be functional , but can also be the first abnormal finding in a patient with significant structural heart disease. The characters of a typical functional heart murmur are ejection in nature; of soft character (grade 1 to 2 over 6); localised at left sternal border, changes with position and with no other cardiac abnormalities detected on examination. A diastolic murmur is never functional even though it may not be significant. The American College of Cardiology class 1 and 2 indications of Echocardiogram for heart murmurs [11] are:
   Class 1: a patient with heart murmur and cardiorespiratory symptoms
   Class 1: an asymptomatic patient with heart murmur in whom there is a moderate probability that the heart murmur is reflective of underlying structural heart disease
   Class 2a: an asymptomatic patient with heart murmur in whom there is low probability of heart disease but in whom the probability of heart disease cannot be reasonably ruled out by physical examination
   The aim of Echocardiogram is to find out the source of the heart murmur, exclude significant structural heart disease, quantifies significance of valvular or structural heart disease and look for associated lesions that will affect the patient's management [11].

2. ECG abnormality
   ECG finding of left ventricular hypertrophy (LVH) or right ventricular strain pattern are indications for Echocardiogram. ECG voltage criteria of LVH is less specific than direct LV wall thickness and LV mass measurement by echocardiogram. High QRS voltage without LVH is seen in young and slim individuals. Abnormal right ventricular depolarisation signal from ECG can be an early sign in patients with potentially fatal arrhythmogenic right ventricular dysplasia (ARVD). Severely abnormal Echocardiographic findings are major criteria for such clinical diagnosis[12]. Moreover, incidental finding of "pathological Q" wave needs corresponding echocardiographic findings for confirmation of old transmural myocardial infarction.

3. Incidental finding of cardiomegaly on CXR (Fig. 6 a,b & c)
   Causes of cardiomegaly on CXR can be due to
   a. left ventricular dilatation
   b. right ventricular dilatation
   c. left, right or biatrial enlargement
   d. underlying valvular heart disease causing such chamber dilatation
   e. pericardial effusion
   f. composite shadow from the lung without true cardiac abnormality
   A simple resting comprehensive echocardiogram is an indispensable test for such differentiation.

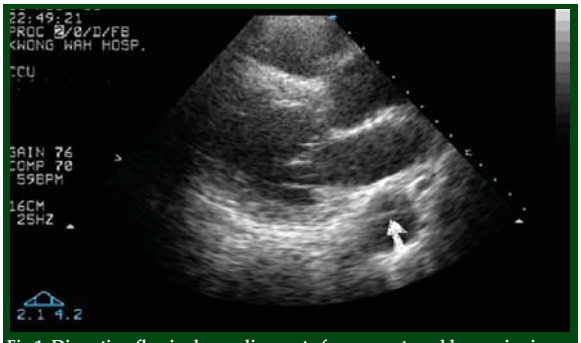

Fig 1. Dissection flap in descending aorta from parasternal long axis view

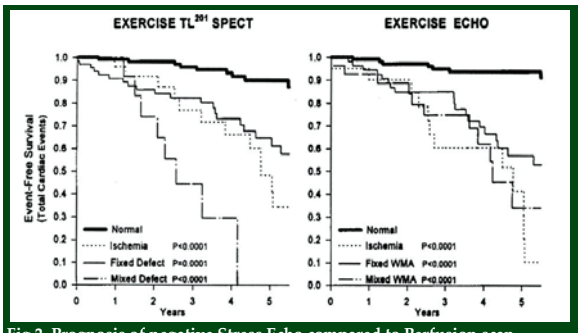

Fig.2 Prognosis of negative Stress Echo compared to Perfusion scan. Olmos, L.I. et al *Circulation* 1998;98: 2679-86

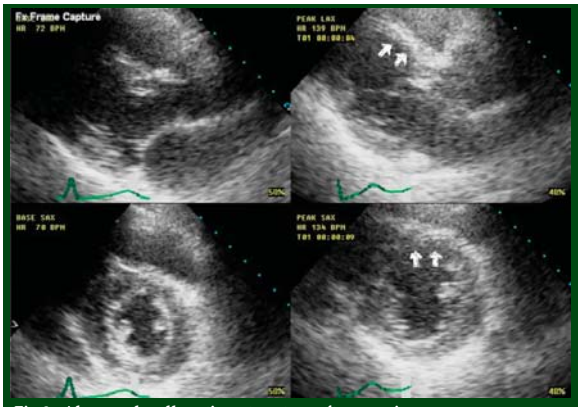

Fig.3a Abnormal wall motion at septum after exercise

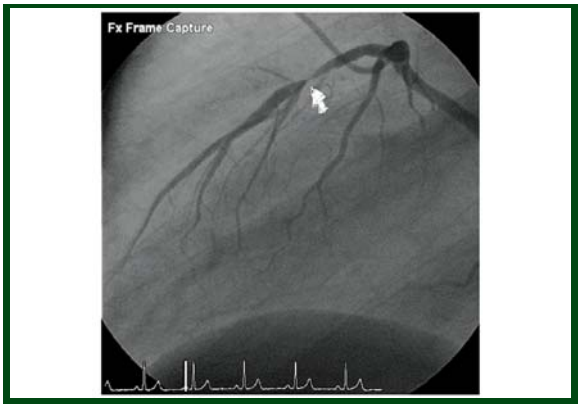

Fig 3b Corresponding angiogram showing tight mid-LAD stenosis

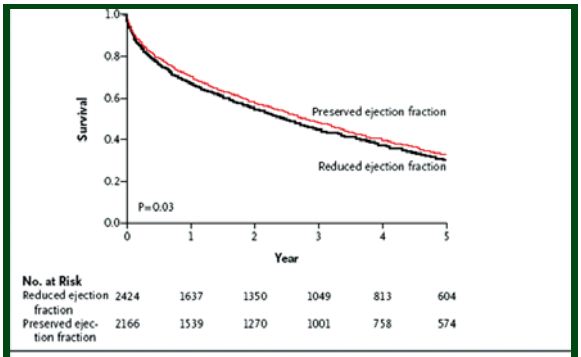

Figure 2. Kaplan–Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction.

Fig. 4 Poor prognosis of patients with diastolic heart failure
Theophilus E. et al, *NEJM* 20 July,06, 355, 251-259

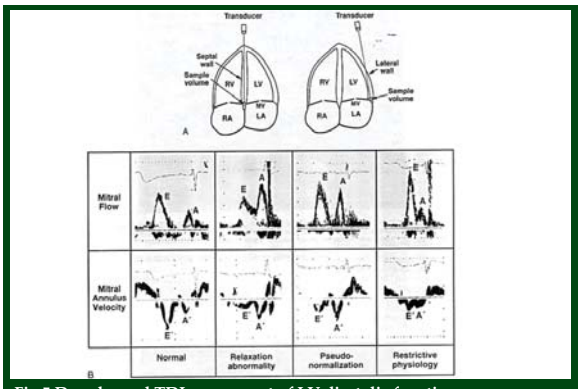

Fig.5 Doppler and TDI assessment of LV diastolic function

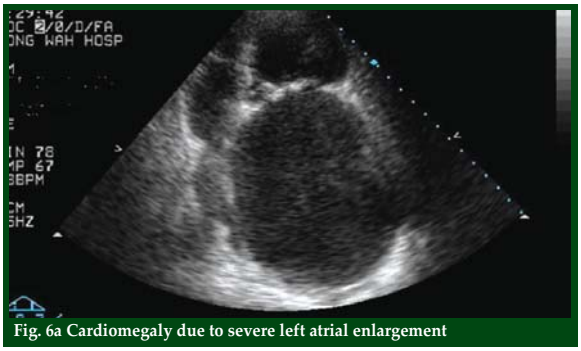
Fig. 6a Cardiomegaly due to severe left atrial enlargement

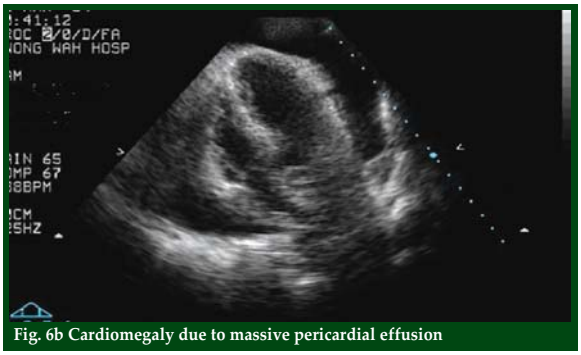
Fig. 6b Cardiomegaly due to massive pericardial effusion

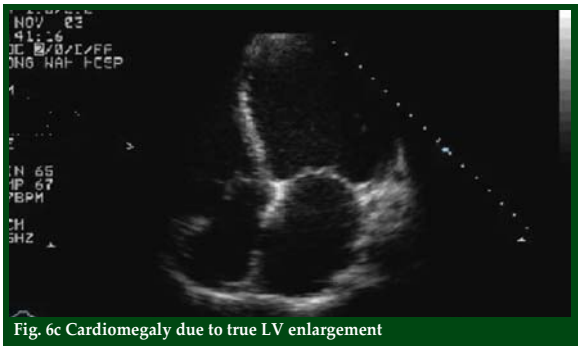
Fig. 6c Cardiomegaly due to true LV enlargement

References

1. Parveen Kumar & Michael Clark. *Clinical Medicine A Textbook for Medical Students and Doctors 3rd Edition* . Bailliere Tindall
2. The ACC/ AHA 2002 Guideline Update for Exercise Testing
3. Fleischmann KE, Hunink MG, Kuntz KM et al (1998) Exercise echocardiography or exercise SPECT imaging ? A met-analysis of diagnostic test performance. *JAMA* 280:913-920
4. WilliamsMJ, Marwick TH, O'Gorman D, et al (1994) Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in woman. *Am J Cardiol* 74:435-438
5. Arruda-Olson AM, Juracan EM, Mahoney DW, et al (2002) Prognostic valueof exercise echocardiography in 5768 patients: is there a gender difference ? *J Am Coll Cardiol* 39:625-631
6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction, *N Engl J Med* 2006; 355:251-259, Jul 20, 2006.
7. Yip GW, Ho PP, Woo KS, Sanderson JE. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. *Am J Cardiol*. 1999 Sep 1;84(5):563-7.
8. Zile MR., Baicu CF., Gaasch WH, Diastolic Heart Failure - Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle, *N Engl J Med* 2004; 350:1953-1959, May 6, 2004.
9. Nagueh SF, Middleton KJ, Kopelen HA, et al Doppler tissue imaging: a noninvasive technique for evaluation of of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997; 30: 1527-1533
10. Nishimura RA, Appleton CP, Redfield MM, et al. Noninvasive Doppler echoacdriographic evaluation of left ventricular filling pressures in patients with cadriomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. *J Am Coll Cardiol* 1988: 11: 1227-1234
11. ACC/AHA/ASE 2003 Guideline Update for Clinical Application of Echocardiography, Sept 3, 2003 issue, *J Am Coll Cardiol*
12. Carol G, Antonio P., et al, Ayyhythmogenic Right Ventricular Cardiomyopathy, *J Am Coll Cardiol*, 2001; 38: 1773-1781

Management of Diastolic Heart Failure

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Case Presentation

A 70 year-old lady with known history of uncontrolled hypertension for years, presented with bilateral ankle swelling and impaired exercise tolerance. Her serum N-terminal pro B-type natriuretic peptide (BNP) was increased. Echocardiogram showed normal left ventricular systolic function but there was presence of left ventricular hypertrophy with diastolic dysfunction. Her symptoms were controlled with diuretics and angiotensin receptor blocker. However, she stopped the treatment by herself after her symptoms had improved. She was finally admitted to the hospital because of acute pulmonary oedema.

Epidemiology

Patients with diastolic heart failure (DFH) are not uncommonly encountered by primary care physician. About 30% to 55% of patients with heart failure have preserved systolic function, often defined as left ventricular ejection fraction (LVEF) greater than 40 to 50%[1-3]. In Asia, due to the high prevalence of hypertension, 50% of patients with heart failure have normal systolic function[4, 5] and the incidence of DHF will further increase due to the aging population. The mortality of DHF is about 5-8% per year[6, 7], which is about half of that of systolic heart failure. In a recent community-based prospective cohort of patients with heart failure, more than half (55%) had preserved systolic function and the mortality of DFH (16% at 6 months) was shown to be comparable to that of systolic heart failure[8]. The morbidity in terms of reduction in quality of life and exercise tolerance, hospitalisation rates and health-care costs per person for both systolic and DHF are similar[6, 9].

Pathophysiology

The clinical manifestations and haemodynamic consequences of systolic and DFH are similar, although the primary pathophysiology mechanisms are different. DFH is caused by left ventricular diastolic dysfunction, leading to increased resistance to left ventricular filling and eventually resulting in heart failure syndrome. Hypertension, diabetes mellitus, and coronary artery disease are common conditions that predispose to the development of DFH. Impaired ventricular relaxation and increased ventricular stiffness are the underlying mechanisms causing diastolic dysfunction. Activation of the renin-angiotensin-aldosterone system plays an important role in the development of myocardial fibrosis and stiffness[10, 11]. Inhibition of renin-angiotensin-aldosterone system has been demonstrated to reduce myocardial stiffness and leads to regression of myocardial fibrosis [12].

Diagnosis of DHF

According to ACC/AHA guidelines, the diagnosis of DFH is based on the clinical findings of heart failure with the findings of preserved LVEF and the absence of valvular abnormalities[13]. The European guidelines require the finding of evidence of diastolic dysfunction[14]. Echo-Doppler assessment is a convenient and effective way of assessing diastolic function. Echocardiogram can also exclude other specific conditions, such as hypertrophic cardiomyopathy, aortic stenosis, infiltrative cardiomyopathies and pericardial disease. BNP, a cardiac neurohormone released by the ventricles in response to volume expansion and pressure overload, has recently emerged as a marker for heart failure[15]. BNP is elevated in systolic and DHF, though more markedly elevated in systolic heart failure[8]. The level of BNP correlates with severity of diastolic dysfunction and is highest among those with a restrictive filling pattern[15]. Study in Hong Kong has shown that N-terminal pro BNP can help in the diagnosis of DHF[16]. Several studies report the use of BNP in the diagnosis of systolic and DHF in the primary care, urgent care, and emergency department settings[17, 18]. It can be used as a screening test to rule out heart failure due to its high negative predictive value.

Principles of Treatment

The current strategy for the management of DHF focuses on symptom relief and modification of underlying causes of DHF. Diuretic therapy is required in symptomatic patients but should be used cautiously, as excessive diuretics may decrease cardiac output and cause hypotension and renal failure. Compared with systolic heart failure, DHF patients require lower doses of diuretics and may tolerate their withdrawal without increasing heart failure symptoms[19]. Tachycardia is very poorly tolerated in DHF, and in the presence of atrial fibrillation, adequate control of heart rate by beta-blockers or calcium channel blockers and maintenance of sinus rhythm are beneficial. Reduction in heart rate

may be associated with improved ventricular filling and haemodynamics. Non-pharmacological measures such as salt restriction, weight control and exercise have been shown to reduce symptoms in patients with DHF[20]. For primary care physicians, hypertension is the most common underlying cause of diastolic dysfunction; therefore, aggressive management of hypertension is essential in the prevention and management DHF. In patients with coronary artery disease, therapies to relieve myocardial ischaemia are also likely to be beneficial.

Specific drugs

It is likely that most of the proven drugs used in treating systolic heart failure (ACEI, angiotensin receptor blockers, beta-blockers, aldosterone antagonists) may also be beneficial in the treatment of DHF[21]. However, evidence-based treatment strategies for DHF are limited. Two large-scale randomized controlled trials have recently provided some evidence for the treatment of DHF. The Candesartan in Heart Failure - Assessment of Reduction in Mortality (CHARM) - Preserved study is a randomized placebo-controlled trial of candesartan (with a target dose of 32 mg daily) in 3023 patients with DHF, NYHA II-IV and an LVEF of >40%[22]. After a median follow-up of 3 years, candesartan group had significantly fewer hospitalisations (HR 0.84: CL 0.70-1.00; p=0.047), and there was a trend towards reduction in the primary composite end point of heart-failure hospitalisation and death from cardiac cause (HR 0.86: CI 0.74-1.00; p=0.051).

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study randomised 850 DHF patients who were over 70 years of age with an LVEF of ≥45% and echocardiographic features suggesting possible diastolic dysfunction to receive perindopril at 4 mg per day or placebo[23]. The primary endpoint was a composite of all-cause mortality and unplanned heart failure related hospitalisation. No significant improvement in the primary outcome was shown, but by 1 year, reduction in hospitalisation for heart failure was observed (HR 0.628, CI 0.408-0.966; p=0.033) and functional class and 6-min corridor walk distance had improved in those assigned to perindopril. This study suggested that perindopril may be of benefit in this patient population.

Conclusion

HF is common and may account for more than 50% of heart failure cases among the elderly. The principles of treatment include symptom relief by judicious use of diuretics, rate control of atrial fibrillation, and aggressive control of hypertension. Limited evidence from randomised control trials suggested that angiotensin receptor blockers and ACEI are beneficial. More evidence-based treatment strategies to enhance the care of this condition will be available when some of the on-going clinical trials are completed.

References

1. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998; 98: 2282-9.
2. Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients ?65 years of age. *Am J Cardiol* 2001; 87: 413-9.
3. MacCarthy PA, Kearney MT, Nolan J, et al. Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study. *BMJ* 2003; 327: 78-9.
4. Sanderson JE, Chan S, Chan WWM et al. The aetiology of heart failure in the Chinese population of Hong Kong - a prospective study of 730 consecutive patients. *Int J Cardiol* 1995; 51: 29-35.
5. Yip GWK, Ho PPY, Woo KS et al. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. *Am J Cardiol* 1999; 84: 563-7.
6. O'Conner CM, Gattis WA, Shaw L, Cuffe MS, Califf RM. Clinical characteristics and long-term outcomes of patients with heart failure and preserved systolic function. *Am J Cardiol* 2000; 86: 863-7.
7. Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. *J Am Coll Cardiol* 1991; 18: 377-82.
8. Bursi F, Weston S, Redfield M, et al. Systolic and diastolic heart failure in the commuity. *JAMA*. 2006;296:2209-16.
9. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002; 288: 2144-50.
10. Zannad F, Dousset B, Alla F. Treatment of congestive heart failure: interfering the aldosterone-cardiac extracellular matrix relationship. *Hypertension* 2001; 38: 1227-32.
11. Zile M, Brutsaert D. New concepts in diastolic dysfunction and diastolic heart failure: part II: causal mechanism and treatment. *Circulation* 2002; 105: 1503-8.
12. Brilla CG, Funck CR, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000; 102: 1388-93.
13. Hunt SA, Baker DW, Chin MH et al. Guidelines for the evaluation and management of chronic heart failure in adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the evaluation and management of heart failure). *J Am Coll Cardiol* 2001; 38: 2101-13.
14. 4European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eu Heart J* 1998; 19: 990-1003.
15. Dickstein K. Natriuretic peptides in detection of heart failure. *Lancet* 1998; 351: 4
16. Ko WC, Leung TC, Choi MC, Chan CK, Tse TS, Tsui KL, Chan KK, Li SK. Brain natriuretic peptide- An emerged tool in assessment of congestive heart failure. *J HK Coll Cardiac* 2006: 14 (Suppl 1), A89.
17. Cowie M, Struthers A, Wood D, Coats A, Thompson S, Poole-Wilson P. Value of natriuretic peptides in assessment of patients with possible heart failure in primary care. *Lancet* 1997; 350: 1347-51.
18. Dao Q, Krishnaswamy P, Kazanerga R, Harrison A, Amirnovin R, Lenert L. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001; 37: 379-85.
19. Van Kraaij DJ, Jansen RW, Bouwels LH, Gribnau FW, Hoefnagels WH. Furosemide withdrawal in elderly heart failure patients with preserved left ventricular systolic function. Am J Cardiol 2000; 85: 1461-6.
20. Kitzman DW, Brudbaker PH, Anderson RA, et al. Exercise training improves aerobic capacity in elderly patients with diastolic heart failure: a randomized, controlled trial [abstract]. *Circulation* 1999; 100: 296
21. Wu EB, Yu CM. Management of diastolic heart failure: a practical review of pathophysiology and treatment trial data. *Int J Clin Pract*. 2005; 59(10):1239-1246.
22. Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; 362: 777-81.
23. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonske L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006; 27(19):2238-45.

Updates on Percutaneous Coronary Intervention

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Ever since the invention of percutaneous coronary intervention (PCI) to treat coronary artery disease (CAD) around twenty years ago, its clinical use has been expanded dramatically. According to overseas and local experiences, the number of PCI performed every year far exceeds the number of patients undergoing coronary artery bypass surgery (CABG). The procedural success, safety and durability of PCI have dramatically improved because of the advance in technology, refinements in periprocedural adjunctive pharmacology (e.g. glycoprotein IIb/IIIa inhibitors, alternative thrombin inhibitors), and a better understanding of early and late outcomes. Indeed, it is now one of the most frequently performed medical procedures.

In this article, I will review the latest advance in the field of intervention cardiology and the different indications of PCI.

Percutaneous Transluminal Coronary Angioplasty (PTCA)

Andreas Gruentzig performed the first balloon angioplasty in human in 1977, using a prototype fixed-wire balloon catheter[1]. Balloon angioplasty expands the coronary lumen by stretching the vessel wall and tearing the atherosclerotic plaque. Meanwhile, longitudinal redistribution of the atherosclerotic plaque contributes to the increase in vessel lumen. PTCA is able to improve coronary flow and hence reduces coronary ischaemia in selected patients. However, the uncontrolled tearing of the atherosclerotic plaque may result in flow-limiting coronary dissections that results in abrupt closure in 5 to 8% of patients[2, 3]. These patients may need urgent CABG in order to salvage ischemic myocardium. On the other hand, elastic recoil of the stretched vessel wall left an average residual stenosis of 30 to 35%, with higher residual stenoses correlated with higher subsequent recurrence rates. Repeat revascularisation by either repeat PTCA or CABG was in the range of 20 to 40%. Hence, the long-term efficacy of PTCA is significantly limited by restenosis. Nowadays, in the era of stent, standalone PTCA is now reserved only for cases such as smaller (<2.5mm) vessels and early anastomotic lesions in saphenous vein grafts in which the long-term benefits of coronary stenting are limited.

Coronary Atherectomy

By removing the obstructing atherosclerotic plaque in the coronary arteries, a larger vessel lumen can be obtained. This may improve the vessel wall compliance and render the vessel more dilatable. Different atherectomy devices are available including directional coronary atherectomy (DCA), rotational atherectomy, transluminal extraction atherectomy and excimer laser coronary angioplasty. DCA uses a directional cutting device to remove the atheroma while rotational atherectomy uses a rotating burr to remove calcified atheromatous plaque. Before the availability of coronary stents, there was huge enthusiasm in the use of these devices in the hope of improving both short and long-term outcomes. However, multiple studies showed standalone coronary atherectomy did not improve the restenosis rate compared with PTCA. In a contemporary cardiac catheterisation laboratory, coronary atherectomy is now being used in less than 10% of cases. DCA may still be used for bulky lesions in the left main and proximal left anterior descending arteries whereas rotablator is occasionally needed to pre-treat rigid and calcified lesions for subsequent stenting.

Coronary stents

The first implantation of coronary stent in human in 1986 has revolutionised the practice of intervention cardiology. By providing a scaffold to the dilated coronary lesion, coronary stents almost completely eliminate elastic recoil which is the major cause of restenosis after PTCA. Achieving a larger vascular lumen, coronary stenting effectively reduces angiographic and clinical restenosis[4, 5]. By tagging up uncontrolled dissection, it also significantly reduces acute closure of the vessel after PTCA. This significantly decreases early ischaemic complications and improves the safety of the procedure.

A large number of randomised trials demonstrated clear benefits of coronary stents over PTCA in different subsets of patients. These included de novo or restenotic lesions, abrupt or threatened closure (i.e. bailout situation), saphenous vein grafts, chronic total occlusion and acute coronary syndromes. Hence these devices are now used in more than 80% of all PCIs.

Despite the improvement in early outcomes, 10 to 20 percent of patients had recurrent symptoms within 12 months after stent implantation. Repeat angiogram usually revealed new tissue formation (neointimal hyperplasia) within the stent. Histological analyses revealed that a great deal of the volume of the in-stent restenotic lesion is made up of "myxomatous" tissue,

comprising occasional stellate smooth muscle cells embedded in a loose and highly hydrated extracellular matrix.

The major risk factors for restenosis are longer lesion length (>30m), longer stent length, small vessel diameter (<2.5mm), smaller post-treatment lumen diameter, reopened chronic total occlusion, ostial and bifurcation lesions, and the presence of diabetes. If multiple risk factors are present, the restenosis rate may be up to 40 to 50%. Even though restenosis seldom causes acute coronary syndrome or cardiac death, patients often need repeated admissions and revascularisation to relieve symptoms. Different systemic medications were tested in clinical trials to lower the restenosis rate but without avail. Radiation treatment (intracoronary brachytherapy), presumably targeting smooth muscle cell proliferation and matrix synthesis, was used to treat in-stent restenosis. In several randomised, placebo-controlled trials, intracoronary brachytherapy showed significant improvement in angiographic and clinical outcome in native coronary arteries and in SVGs[6,7,8,9]. However, recent data showed that there was a late increase in restenosis and clinical events among those received brachytherapy. Most if not all interventionist had stopped using brachytherapy for s few years already. Drug eluting stent, as described below, is now the mainstay of therapy for restenosis.

Drug Eluting Stent (DES)

The idea of combining a coronary stent and an anti-proliferative drug is to target the different components of restenosis. By achieving a bigger post-procedural vessel lumen, the use of bare metal coronary stent reduces both clinical and angiographic restenosis. As said before, 20 to 30% of these patients have recurrent symptoms due to neointimal hyperplasia which is a "normal response" to vascular injury. A number of systemic agents have been used to prevent restenosis after balloon angioplasty and stenting, but none has had a consistent effect on restenosis prevention. By local delivery of a highly efficacious anti-proliferative drug, DES is very effective at suppressing the local neointimal proliferation. Angiographic and clinical restenosis in general have been reduced to less than 10% and 5% respectively[10,11,12,13]. Some DES systems (e.g. sirolimus, everolimus, polymer-delivered paclitaxel) have, in clinical studies, significantly reduced restenosis whereas other had no or a limited effect (e.g. batimastat, dexamethasone, stent-based paclitaxel) or were clinically detrimental (e.g. actinomycin D, 7-hexanoyltaxol). It demonstrated the important interaction between the stent design, the presence or absence of a polymeric coating that is used to deliver the drug, and the types of agents that are delivered to the vessel wall.

The dramatic reduction in restenosis allowed interventionist to expand the application of PCI to different subsets of patients. Patients who were at high risk for restenosis in the bare metal stent era (e.g. diabetic patients with multivessel diseases, left main disease) may now consider PCI as an option to CABG figures. Indeed, a recent study showed that multivessel PCI with DES might be as good as, if not better than, CABG.

Recently, there is a hot debate around the issue of late stent thrombosis associated with the use of DES. By implanting a metallic stent in the blood stream, there will be continuous activation of the flowing platelets which may result in platelet clump and then blood clot formation. This may cause acute closure of the stent and patient would then present with ST elevation MI. The risk is substantially reduced when endothelialisation (i.e. the stent luminal surface was covered by a thin layer of endothelium) is completed. This will take around four weeks for a bare metal stent. The use of dual anti-platelet agents (i.e. aspirin plus ticlopidine or clopidogrel) has been proven to reduce the incidence of stent thrombosis significantly. For DES, the anti-proliferative drug will act on not only smooth muscle cells but also endothelial cells. Hence, the process of endothelialisation for DES is much prolonged. For bare metal stent, it is recommended to take both aspirin and clopidogrel for at least 4 weeks. On the other hand, the recommended duration of dual anti-platelet agents for DES is 6 to 12 months.

Recent data showed that, after stopping dual antiplatelet agents, there was an increase in late stent thrombosis in those patients who were treated with DES compared with those treated with bare metal stents. However, a further look at the data showed that there was no increase in myocardial infarction and, most importantly, death in the DES arm. Indeed, a review of DES by the US FDA suggested that DES was safe and beneficial to the patients. It recommended a prolonged duration of dual anti-platelet agents so as to prevent late stent thrombosis.

Distal Embolic Protection Devices

Although distal embolization of atherosclerotic debris was thought not to be a problem during the early years of catheter-based intervention, it is now recognised as a potential cause of distal myocardial necrosis after PCI. The role of distal embolisation is particularly important in SVG and acute coronary syndrome. It is also now recognised as a cause of neurological complication after carotid stenting.

There are three different types of distal protection devices. The first involves distal occlusion using a low pressure balloon[14]. Any debris liberated by intervention remains trapped in the stagnant column of blood and can be aspirated before the occlusion balloon is deflated to restore antegrade flow. The second class consists of distal filters that are passed across the target lesion in their smaller collapsed state, opened to approximate the edges of the filter material against the vessel wall, and remain in place to catch any liberated embolic material larger than the filter pore size, until they are collapsed after stent deployment, thereby removing the captured embolic material from the body[15]. The third type involves proximal occlusion of the treated vessel with balloon. Any debris liberated can then be aspirated from the guiding catheter.

These devices have been studied in SVG and been proven to reduce post-procedure complication significantly. However, data on ST elevation MI were inconsistent. The use of these devices in carotid stenting is under extensive study right now. In short, there are mounting evidence that distal atherosclerotic debris commonly embolises from lesions in many vascular

territories during PCI, that it can be recovered using any of the three types of embolic protection device, and that use of those devices reduces the incidence of end-organ injury.

Indications for PCI

Patients with No or Mild Angina

Patients who are asymptomatic or have only mild symptoms are best treated with medical therapy unless one or more significant lesions subtend a moderate to large area of viable myocardium, the patient prefers to maintain an aggressive life style or has a high-risk occupation, and the procedure can be performed with a high chance of success and low likelihood of complications[16]. PCI should not be performed in patients with absent or mild symptoms if only a small area of myocardium is at risk, if no objective evidence of ischaemia can be found, or if the likelihood of success is low or the chance of complications is high.

There is no evidence so far that PCI of a haemodynamically insignificant "vulnerable" plaque prevents a subsequent MI.

Patients with Moderate or Severe Angina

Patients with moderate or severe angina are suitable candidates for PCI provided that the lesion subtends a moderate to large area of viable myocardium[16]. PCI should be offered even if they have a higher risk for an adverse outcome with revascularisation.

Patients with Unstable Angina or Non-ST elevation Myocardial Infarction

Before the availability of glycoprotein IIb/IIIa inhibitors and coronary stents, clinical studies could not document any benefit of early invasive therapy in patients presented with unstable angina or non-ST elevation MI[17,18]. However, recent trials, with the use of both glycoprotein IIb/IIIa inhibitors and coronary stents, showed that early invasive treatment (i.e. cardiac catheterisation and revascularisation) could reduce the rate of death, myocardial infarction or urgent revascularisation[19]. These benefits were highest in high risk patients (e.g. those with rest pain, cardiac enzyme elevation, or ECG changes). Hence, patients now presented with unstable angina or non-ST elevation MI are generally advised to undergo cardiac catheterisation and PCI if needed.

Patients with ST elevation Myocardial Infarction

Patients with ST elevation MI have thrombotic occlusion of the culprit coronary artery. It is well proven that early reperfusion by fibrinolytics could limit the infarct size and could hence prolong survival and improve prognosis. It is now generally accepted that catheter-based reperfusion (i.e. primary PCI) is preferable to fibrinolytics if facility and expertise are available. This is because primary PCI allows more rapid, complete and sustained reperfusion. Meanwhile, it also allows treating the residual coronary lesion which probably would cause myocardial ischaemia if left alone. Invasive strategy also allows better delineation of the coronary anatomy and hence better risk stratification. Most importantly, primary PCI is associated with less mechanical complication (e.g. myocardial rupture, acute mitral regurgitation, ventricular septal defect) and thrombolysis-related intracranial haemorrhage which is usually fatal.

Conclusion

PCI is one of the most frequently performed medical procedures. With the improvement in hardware and accumulation in clinician's experience, its usage and indications are ever expanding. The availability of DES allows more difficult subset of patients to be treated by this catheter-based procedure. Prolonged duration (1 year) of dual anti-platelet therapy after DES is recommended. Patients with unstable angina, non-ST elevation MI, ST elevation MI and moderate to severe angina symptoms should consider PCI as the treatment of choice. Their symptoms and prognosis would be significantly improved after this invasive procedure. For those with no or minimal symptoms, they are candidates for PCI if there is objective evidence of significant myocardial ischaemia. Otherwise, medical treatment with aggressive control of cardiovascular risk factors should be considered.

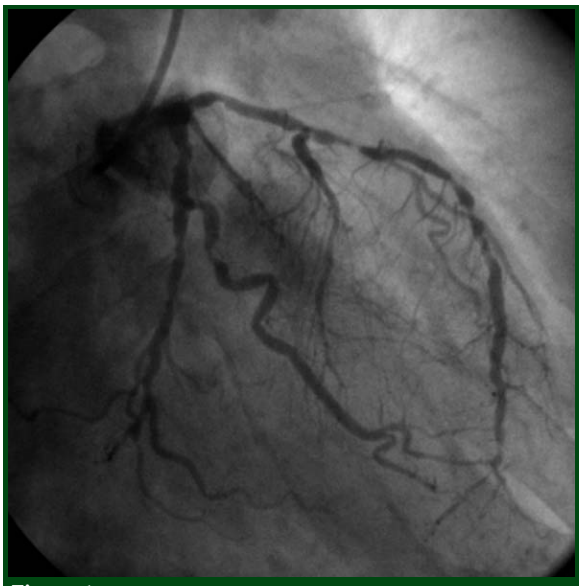

Figure 1a

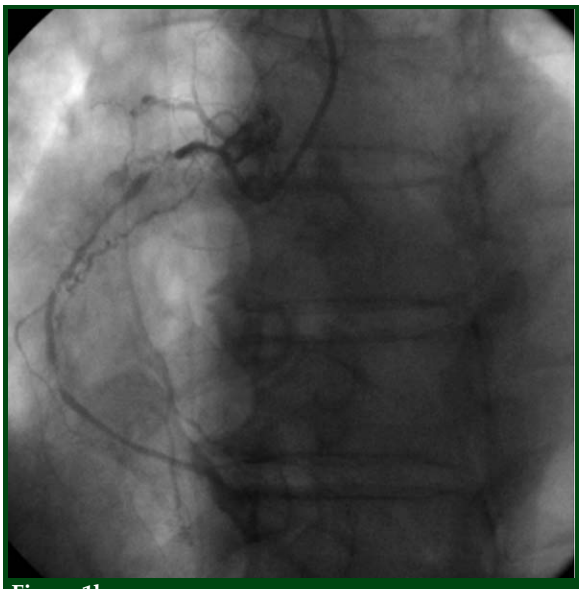

Figure 1b

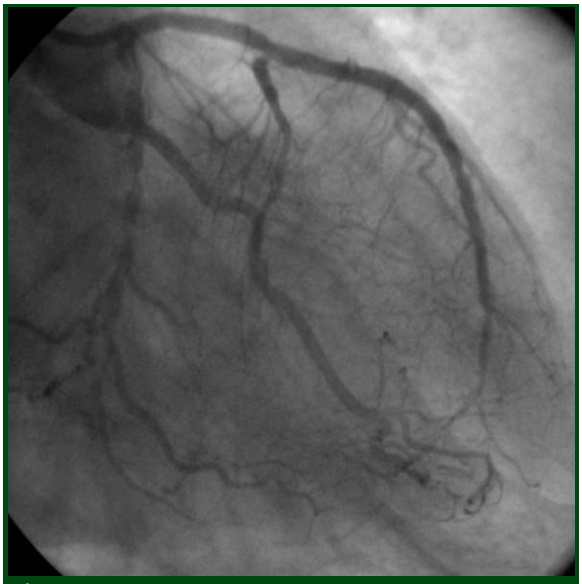

Figure 1c

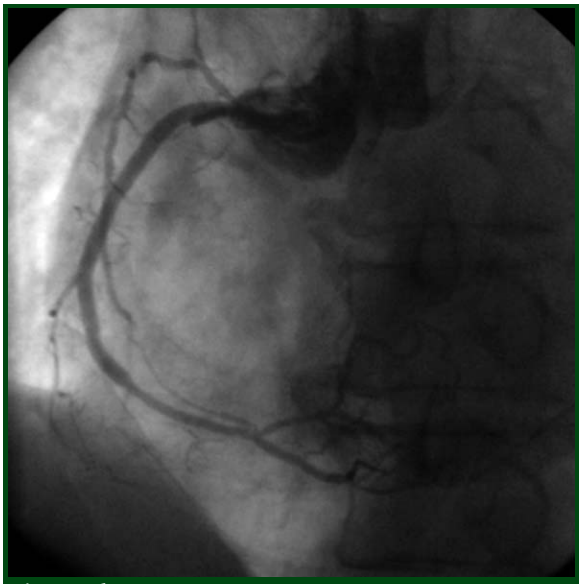

Figure 1d

Figure Legends

This 72-year-old gentleman with history of hypertension and hypercholesterolaemia presented with typical angina. Cardiac catheterisation showed critical stenoses in proximal, mid and distal left anterior descending artery (LAD), first obtuse marginal branch (OM1) & distal left circumflex artery (1a), and subtotal occlusion of the right coronary artery (RCA) (1b). Without DES, the patient had a high restenosis rate and CABG would be a preferred option. This patient subsequently underwent PCI with deployment of 3 DES in LAD (1c), 1 DES in OM1 (1c) and 3 DES in RCA (1d). The plan was to continue life-long dual anti-platelet therapy.

References

1. Gruentzig AR. Translumination dilatation of coronary artery stenosis (letter). *Lancet* 1978;1:263.
2. Lincoff AM, Popma JJ, Ellis SG, et al. Abrupt vessel closure complicating coronary angioplasty: Clinical, angiographic, and therapeutic profile. *J Am Coll Cardiol* 1992;19:926-935.
3. Kuntz RE, Piana R, Pomerantz RM, et al. Changing incidence and management of abrupt closure following coronary intervention in the new device era. *Cathet Cardiovasc Diagn* 1992;27:189-190.
4. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994;331:496
5. Serruys PW, van Hout B, Bonnier H, et al. Randomized comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary aartery disease (Benestent II). *Lancet* 1998;352:673.
6. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997;336:1697.
7. Waksman R, White R, Chan R, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation* 2000;101:2130.
8. Leon M, Teirstein P, Moses J, et al. Localized intracoronary gamma radiation therapy to inhibit the recurrence of restenosis after stenting. *N ENgl J Med* 2001;344:250.
9. Popma J, Suntharalingam M, Lansky A, et al. Randomized trial of 90Sr/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation* 2002;106:1090.
10. Morice M, Serruys P, Sousa J, et al. A randomized comparion of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773.
11. Moses J, Leon M, Popma J, et al. Angiographic and clinical outcomes after a sirolimus-eluting stent compared to a standard stent in patients with complex coronary stenoses. *N Engl J Med* 2003;349:1315.
12. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108:788.
13. Stone C, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221.
14. Baim D, Wahr D, George B, et al. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 2002;105:1285.
15. Stone Gw, Rogers C, Hermiller J, et al. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of a diseased saphenous vein aorto-coronary bypass graft. *Circulation* 2003;108:548.
16. Smith S, Dove J, Jacobs A, et al. ACC/AHA guidelines of percutaneous coronary interventons - Executive summary. *J Am Coll Cardiol* 2001;37:2215.
17. Anderson H, Cannon C, Stone P, et al. One year results of the Thrombolysis In Myocardial Infarction (TIMI) IIIB clinical trial: A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. *J Am Coll Cardiol*. 1995;26:1643.
18. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;338:1785
19. Cannon C, Weintraub W, Demopoulos L, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879.

A Brief Review of CT Coronary Angiogram

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Introduction

Helical computed tomography (CT) started in the years of '90, enable faster scan acquisition and faster data reconstruction. Multislice CT (MSCT) is the latest technology in this decade, functioning by acquiring multiple simultaneous slices using multi-detector system. Most advanced and contemporary models are the 64-slices machine, dual source CT machine and the 256-slices machine. The last-mentioned machine model, which is still on-trial, will be coming to the market soon. All these machines are competing for better performance by improving the spatial and temporal resolution. To date, a good CT machine can complete the scan in less than 10 seconds in optimal settings.

Indication for CT Coronary Angiogram

Framingham risk stratification alone is unable to confirm coronary artery disease. Other functional tests have the sensitivity and specificity of about 70-80% in detecting ischaemic heart disease. Compared with invasive coronary angiography for detection of significant lesions, segmental based sensitivity, specificity, and positive and negative predictive value of MSCT are 95%, 98%, 87% and 99% respectively (JAMA 2006; 293:2471-2478). General indications of CT Coronary Angiography are the asymptomatic patients with 2 or more cardiovascular risk factors, diabetic patients, patients without typical chest pain but abnormal treadmill stress test, post-CABG patients to assess the graft, patients with acute chest pain at the emergency department and those with anomalous coronary arteries.

Patients who are NOT considered for cardiac CT imaging are those with typical angina and strongly positive treadmill test, patient with renal dysfunction, known allergy to contrast media and young patient without any coronary risk factors.

The ACC guidelines suggest that screening for calcification may be of value for an individual who is considered to be at intermediate 10 year risk which is defined as a 10% to 20% likelihood of a cardiac event within the next 10 years (Circulation 2000).

Another role of cardiac CT is for RF (Radiofrequency) ablation planning. CT helps to provide a clear and accurate anatomy prior to ablation, especial in atrial fibrillation ablation. By integrating the CT images and Mapping system, it allows precise and shorter time of ablation.

CT is also useful in defining the coronary sinuses anatomy prior to CRT implantation.

Physical Principle and Practical Issue

Scan resolution

The 16/64 slices CT machine with narrow scan collimation provide reconstructed data that are isotropic. An isotropic voxel is a cube measuring the same x, y and z planes. That means an identical spatial resolution in all planes. This property significantly enhances the reconstruction work of CT Coronary Angiogram.

Radiation dose and Risk

As the number of slices increase, radiation efficiency also increases. Radiation dose is affected by mAs (electric current of the machine) and kVp and both have to be kept as low as possible. The radiation doses of coronary angiogram by a 16-slice and 64-slice CT machines are approximately 8-10 mSv and 13-18 mSv respectively. (Hunold et al Radiology 2003, Raff et al Jacc 2005)

Radiation risk of 14mSv is about 0.07% life time risk for inducing fatal cancer.

The risk of developing severe allergic reaction with non-ionic contrast is about 0.2%-0.7% of patient.
Please be reminded that the background radiation dose that we receive each year from the sun and soil is about 3-4mSv and is indeed equivalent to about 300 chest radiographs. Single CT coronary angiogram is about 3 to 6 times the yearly radiation dose.

Spatial Resolution

A good spatial resolution is important as we are scanning coronary arteries which have diameter between 1mm to 4mm. To differentiate a 10%-20% coronary stenosis, we need an isotropic spatial resolution of at least 0.3mm or less. The spatial resolution of about 0.33-0.35mm is obtained by a 64-slice machine, with the isotropic voxel geometry of 0.5mm, and seems to be working good!

Temporal resolution

In order to image the rapid cardiac cycle, we need a good temporal resolution. Similar to photography, shorter temporal resolution means that we can catch the image at an almost frozen motion. Ideal temporal resolution should be less than 50msec. For complete motionless imaging of heart, we need the temporal resolution to be 20msec. Better temporal resolution can be achieved by faster gantry (CT machine) rotation.

However it is eventually limited by the mechanical factors, and related to the weight of the whole machine. Other method to improve the temporal resolution include segmental/multi-segmental reconstruction with ECG Gating and more recently, the dual source CT technique. The retrospective ECG Gating algorithm/retrospective data reconstruction can further deal with the challenge of rapid cardiac motion.

Beta Blockers
The purpose of using beta blockers is to decrease the heart rate, so as to improve the temporal resolution. It also lowers the cardiac motion, lowers the cardiac output and therefore improves the contrast enhancement of the coronary arteries. Ideally the heart rate suitable for imaging should be less than 75bpm and being optimal at about 65bpm. We should be aware of the side effects and contraindications of beta blockers.

Breath hold
Purpose of breath holding during the scan is to reduce motion artifacts related to breathing. It is no longer a challenge nowadays using the 64-slice machine, and we need patients to hold their breath for less than 10 seconds. Breath holding period will be even less for more advance machines like dual-source or 256-slice machine. Actually longer breath holding may have influence to the heart rate.

Contrast Media and Injection Design
Non-ionic water soluble contrast (370mg/ml concentration) is used for injection, usually at right upper limb (providing short pathway towards the heart), preferably at the antecubital vein, to facilitate a higher injection rate of 4ml/sec. Good washout of contrast from the right heart can be achieved by saline chaser, and further hastens arrival of contrast and increases the peak enhancement by 30%.

The design of Dual-Flow Contrast Injection helps the Cardiac Function Analysis by improving the right heart visualisation.

Post-acquisition Data Processing
Under the property of retrospective ECG gating, different segments of data are available for reconstruction. The principle is to select the best imaging quality for a particular coronary artery at a specific segment. That is to review various segments for a particular vessel, apply the appropriate filter and window setting.

The tools of post-processing include Maximal Intensity Projection (MIP), Volume Rendering (VR) (Figure 1 & 2), Curve Planar Reconstruction (CPR) (Figure 3 to 6) or Multiplanar Reconstruction (MPR), 3D and cine loop. Radiologist or Cardiologist can apply different tools in the processing for each vessel.

Clinical application

Calcium scoring
Basic assumption is that the calcium load is proportional to the atherosclerotic plaque burden in the coronary arteries. It is well known that coronary artery calcification is a reliable sign of chronic atherosclerotic change and the calcified plaque is not amorphous or dystrophic calcification. High calcium scores pose an extremely elevated risk of hard cardiac events (Wayhs et al Jacc 2002;39:225) and therefore helpful in risk stratification. There is a strong prognostic value of calcium scoring (Guerci A, JACC 2003). Calcium scoring also has a role in monitoring therapy for those patient who are taking lipid lowering therapy or statin (Circulation 2002: 106:1077-1082). However the pitfall is that absence of calcium does not imply absence of atherosclerosis.

Methods of calcium load assessment include the Agatston score, volume scoring and mass scoring.

Assessment of Coronary Stenosis
There are methods to assess stenosis, including eye-balling which is a qualitative assessment, direct measurement on cross-section MPR or long axis MIP, and using automated vessel analysis software programme. The latter two are quantitative methods.

Most studies used a threshold of 50% luminal stenosis to define clinically significant stenosis, while the coronary flow reserve is not affected till the lumen is narrowed by 70-75%. The low threshold of 50% luminal narrowing decreases the likelihood of failing to identify patients in whom cardiac catheterisation is needed. Each stenosis should be assessed in at least two orthogonal views, and only the lumen is compared but not the wall.

In general CT tends to over-estimate the degree of stenosis due to the exaggerated partial volume averaging effect in order to assess the small-sized coronary arteries (Am J Cardiol 2005;96:784-787, JACC 2005;46:552). Other factors contribute to the difference are the difference in measurement techniques and difference of inter-observer agreement on estimation.

Imaging of Bypass Graft
Arterial grafts can be harvested from the left internal mammary artery (LIMA) connecting to the left anterior descending artery (LAD) or from the inferior epigastric artery to the right coronary artery (RCA). On images, the multiple metallic clips are the hints of previous grafting. Venous grafts are usually connecting from the ascending thoracic aorta to the LAD, Diagonal branch or obtuse marginal branch etc. Graft is usually well seen due to be relative less cardiac motion artifacts. We do need to be aware of the rather 'high' location of origin of graft, eg. LIMA graft. For the totally occluded graft, the graft is not well visualised since no luminal contrast is present, and we can only see the graft nipple which is the origin of the graft. Graft stenosis is usually well assessed due to its little motion artifact.

Imaging of Stent
Restenosis is still a major hazard and CT Coronary Angiogram is able to assess patency. In general stent which is made of tantalum and gold will produce more blooming artifact. Strut thickness, and of course the size of the stent, play important role by producing more blooming artifact. Larger size with relative less percentage of strut thickness will enable better visualisation of the lumen. Using a more sharp Reconstruction Kernels may improve stent visualisation.

Stent occlusion is relatively easy to diagnose when the stent lumen appears darker than the enhanced vessel lumen proximal to the stent, associated with absence of enhancement in distal vessel lumen.

Instent stenosis is suspected or considered if there is a dark rim inside the stent and the luminal diameter is reduced by more than 50%. This diagnosis can confidently be made by the 64-slice detector machine for stent larger than 3mm calibre.

Practical Tips

Setting up one's routine when reviewing the images would be very useful. Try to use the tools available (VR, MIP, MPR/CPR) to review each artery. Look at the calcium score, you may need to give up some arterial segments which are heavily calcified. Beware of arterial calcification.

Stenosis has to be reviewed by different orthogonal planes before establishing the diagnosis. Grade the stenosis by luminal narrowing, and not to be influenced by the plaque, in order to avoid over estimation. In reverse, if there is no plaque, think about whether there is really a stenosis. Usually 70-75% are the best segment for slow heart rate, but try to review other segments if a lesion is suspected.

Prospective

Cardiac Function Analysis

By producing cardiac MPR images, the cardiac functional analysis can be done by software. The size or volume of the heart chambers can be measured at respective cardiac phase and the ejection fraction can be calculated. Cardiac wall motion can be analysed at a particular plane at a particular phase of the cycle and therefore any focal wall motion defect can be depicted. Studies have shown some good correlation between the CT and MR concerning the left ventricular (LV) function analysis (Radiology 2004:230 403-410); but the LV volume seems to be significantly higher, and ejection fraction and cardiac output be estimated significantly lower by Cardiac CT as compared with MRI in another recent finding (ECR 2006), ?related to the use of beta-blocker.

Myocardial Perfusion using MSCT

Studies are in progress and mostly on animal models. Results of MSCT are comparable with MRI in detection and sizing of myocardial infarction. However work needs to be done on stress induced myocardial ischaemia.

Plaque Imaging

MSCT can detect both soft plaque and calcified plaque and this is better than conventional cardiac catheterisation. Studies have shown that MSCT is not as good as Intravascular ultrasound (IVUS) in assessment of plaque volume (JACC 2005 46:147-154). However the CT may be helpful in characterising the plaque nature by assessment the density. We are still working on accurate differentiation of high lipid content plaques from fibrous plaque; depiction of culprit plaque with high lipid content and classify those vulnerable plaques.

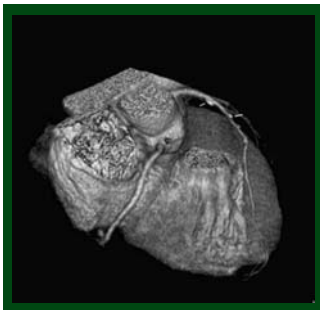


Figure 1

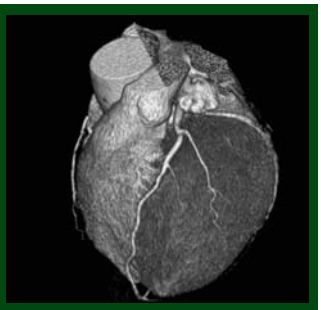


Figure 2

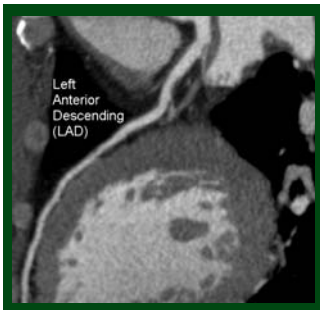


Figure 3

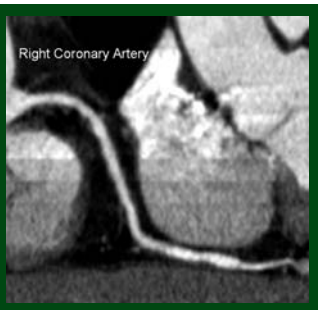


Figure 4

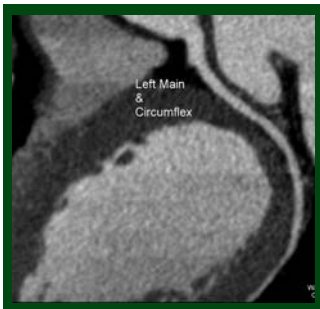


Figure 5

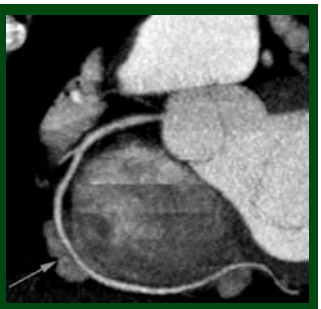


Figure 6

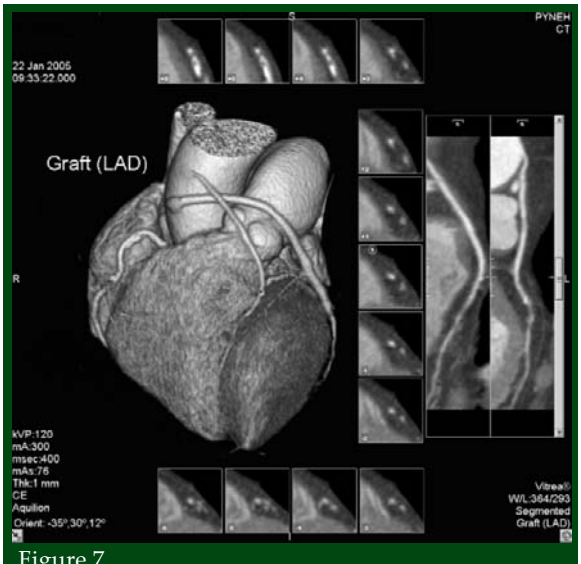


Figure 7

中國古陶瓷之收藏 - 給入門者的一些建議

葉承標醫生

葉承標醫生

英國倫敦大學醫學士, 英國皇家內科醫學院院士,
英國愛丁堡皇家內科醫學院榮授院士, 香港醫學專科學院院士(內科)

心臟科專科醫生

中國陶瓷之歷史可謂源遠流長，至今已有數千年之歷史。自遠古時代之陶器如龍山文化，仰韶文化，然後發展至周朝之原始青瓷，此乃越窯青瓷之始祖。到了兩晉時更有多色釉之出現, 唐三彩是中國陶器之代表作，甚爲外國收藏者之喜愛。到了宋朝中國瓷器更是百花齊放，這時期爲中國陶瓷之一高峰，有五大窯(汝,宮,哥,定,鈞)和八大窯系(加上耀州, 龍泉，青白或影青)之出現，此外建窯和吉州窯亦不乏精采的代表作，名窯中的精品不乏中外陶瓷收藏者所問津，元青花代表青花瓷器之達至成熟，去年一元朝青花大罐"鬼谷子下山"就曾創下逾二億港元之天價成交。而明及清朝之官窯瓷器在最近十數年之價格再創高峰，其價值亦常遠超宋瓷之精品。

中國之瓷器在宋元時期已有外銷。故在土耳奇之博物館藏有豐富及精美之元青花瓷。主要是作爲日常用品如餐具。但真正令歐洲人欣賞從而收藏中國瓷器卻是自英法聯軍於一八六零年之第二次鴉片戰爭時將大量精美之官窯瓷器從北京，天津帶回國從而傳入西方。英人 A. Morrison 就從英軍軍官買入了大量 "戰利品"。 其他藏家如法國人 E. Grandidier 亦有大量之收藏，並其後損贈予巴黎之國家博物館(現藏巴黎居美東方博物館)。十九世紀末歐洲開始有收藏家專門收藏中國瓷器，其中有名的包括英國的Sir P. David, A. Clark, G Eumorfopoulos，美國人 W. Cox，瑞典的 G. Lindberg，他們都是舉世聞名的收藏家， 在上一世紀對中國瓷器在國外之發揚光大有很大的貢獻。

中國瓷器之品種很多，五花八門。是一門很大的學問，所以筆者認為若要成為成功的收藏家，則自己要在以下的方面下功夫：

1. 要研究中國陶瓷之歷史，使自己對各種不同的名窯有一定程度的了解和認識。
2. 要多閱讀可靠的有關古瓷的書籍，比方如北京故宮博物館，台北故宮博物館，國內各大博物館，大英博物館包括 Victoria & Albert Museum的出版都是很可靠的。反之某些私人出版之藏品書籍亦作爲參考, 但質素則有參差。
3. 要到大博物館看實物，比方英國倫敦大英博物館，倫敦大維德基金會 (Percival David Foundation，屬於倫敦大學東方研究中心)，法國巴黎居美東方藝術博物館, 中國北京故宮博物館，上海博物館，台北故宮博物館，美國紐約市大都會博物館等都有著很豐富的陶瓷精品。香港尖沙嘴文比中心旁之展覽館亦不時有古瓷展出，讀者可留意，雖然是隔著玻璃看而不是可以上手仔細研究如重量，和用放大鏡檢查釉之特徵，但要對古物之形制有深切之認識乃是鑒定陶瓷的一種極重要的基礎，不容忽略。
4. 香港一年兩次Sotheby 及 Christies 都有舉行拍賣，入場看拍賣品都是免費的。有些拍品更是以往名收藏家之藏品。但香港之拍賣主要是明清瓷，高古瓷較少。
5. 當然鑒定是一項實戰，不能只是紙上談兵。要多看實物，不只是真的東西，就算是仿品也要看，特別是高仿，要知道仿品之技巧在不斷地進步，有些幾可亂真。
6. 找有經驗的朋友幫眼, 筆者認爲這一點甚重要。

中國古瓷品種很多，五花八門，對收藏家來說選擇甚多，有些喜歡高古瓷 (明代之前之古瓷) 的古樸，而有些則喜愛豔麗的明清瓷。這就等於選美，各花入各眼，沒有一定的標準。至於要決定一件瓷器是否在考慮購買之列，可以從下六點著手 ：

1. 真 ; 如果連真假也不能弄清楚或不能肯定。那麼其他就不用說了 ！ 遇有任何疑點也要重新評估。有時候用科學熱釋光檢驗(thermo luminescence testing) 也有幫助。
2. 名窯與否 ： 名牌校應不容忽視，如宋之五大窯及八大窯系, 唐三彩，越窯秘色瓷，元青花，明清官窯等。它們的升值潛力肯定比較高及受收藏家之歡迎。物品爲以住名收藏家所擁有亦甚爲重要。
3. 完美程度高 : 通常明清瓷的要求完美度要比高古的高。一般來說小量的瑕疵及小量的修補是可以接受的，特別是罕見的形制。但大量修補就不太理想. 筆者深信殘物件現在或將來都不會值大錢。但如果用平價來入作研究途則無不可。
4. 形制是否罕有，很簡單 : 物以罕爲貴。
5. 物件有美感否 ： 這一點有一些主觀成分，但一般不會離開釉色，窯口，手工等。
6. 價錢是否合理，不要忘記數年前的價錢和今天的價錢不一定是一樣，古瓷是常會升值的。

對於新入門的有興趣收藏的讀者，我有下列的建議

1. 因爲古瓷範圍很大和廣，是一門大學問。要精於每一朝代的各種品種是非常困難，故在實際上集中研究及專攻一門是比較可行以及符合邏輯，與此同時更可集中火力來收藏精品。收藏家應先花一段時期來發掘或找出自己的喜好，

不應心急入市.

2. 要留意市場情況以及自己的經濟實力。例如一些瓷器品種極少在市場出現，如宋瓷之汝窯在世上如鳳毛麟角，哥，宋官窯之數目亦甚少。大部份都是在博物館裏。要收集差不多是不切實際或可行性不高。故此無論財力有多豐厚亦無法實行收藏汝，哥，官窯的夢想。一些明清朝代的官瓷動不動要數百萬或千萬，如果要收藏，一兩件就可能要收手，除非財力極其豐厚。
3. 精品的價值上揚較大，就如豪宅一樣，價值長升長有。反之一般的藏品上升空間通常不及精品。我建議有興趣收藏的讀者要收藏自已欣賞及喜愛的品種，不要只是在投資，投機或增值方面著想。也有收藏家花了數年時間收藏，也收藏了不少東西，但卻一件比較有代表性的藏品也帶不出來， 我認爲這有些不太理想。
4. 真正的專家靠自己的一對眼睛來分辨東西的真假和優劣, 別的才靠耳朵去聽別人或專家的介紹。聽專家 (特別是沒有利益衝突的) 的意見作爲參考在某些情況上甚爲重要。筆者期望各位讀者可以成爲自己有興趣收藏品種的專家。
5. 萬事起頭難；要成爲古瓷專家需要時間，好幾年的先陰。從博物館，書籍，看實物，到大賣行 (Sotheby，Christies)的預展，找到商譽好的古董店看實物, 找專家朋友一起研究 "班馬"，都是必經之階段。買了錯東西不要灰心，差不多所有收藏家都曾"交學費"! 經驗很多時是由錯誤累積得來的。
6. 近數年明清瓷特別是官窯漲價不少，有點高處不勝寒的感覺。筆者比較看好宋瓷之精品，特別是名窯，認爲上升空間較大，現在仍然"抵買"。但香港拍賣行主要集中明清官窯瓷, 高古瓷則在倫敦和紐約比較多。
7. 隨著中國近年經濟大幅增長，國民的收入大爲改善。收藏家的數目也大幅上升。古瓷精品 (特別是名窯) 愈來愈難求，價格也只有不斷向上。要找商譽好的古董商店來買，拍賣也是另一途徑。

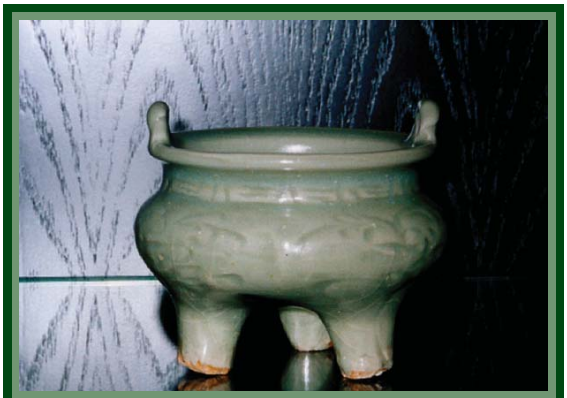
總之，收藏有時如尋寶，有時遇到了一些患真患假的東西又是一種挑戰，祝各位讀者尋寶成功 ！

鳴謝有明堂和鉅滙公司提供之寶貴意見


筆者收藏之明萬曆五彩琴棋書畫高足杯


筆者收藏之唐三彩絞胎手枕


筆者收藏之南北朝越窯蓮花小碟


筆者收藏之元龍泉窯三足香爐

Family Medicine Unit
Department of Medicine
The University of Hong Kong

2007-2008 Part-time Postgraduate Diploma in Community Geriatrics
社區老年醫學 深造文憑

- Quotable qualifications by the Medical Council of Hong Kong
- Clinically orientated
- Multiple learning modes
- Clinical teaching at sites across Hong Kong

This programme will help you upgrade your knowledge and skills in the care of the elderly. The Course, developed in conjunction with Hong Kong Geriatrics Society, will use different modes of study: distance learning, interactive workshops and clinical teaching. Flexible teaching hours and multiple clinical teaching sites will allow you to choose the times and places that suit you best.

2007 - 2008 Part-time Postgraduate Diploma in Community Psychological Medicine
社區精神醫學 深造文憑

This programme will help you upgrade your knowledge and skills in the care of patients with psychological problems. The Course, organized in conjunction with the Department of Psychiatry, will employ different modes of study: seminars, case discussion, clinical training in psychotherapy and clinical teaching by specialist clinicians at various psychiatric and primary care outpatient clinics and rehabilitation facilities.

The two programmes will commence in September and last for one year on a part-time basis of half a day per week.
Tuition fees for the whole programme are HK$42,000, subject to adjustment in 2007/08.

Closing date for application: **30th April 2007**

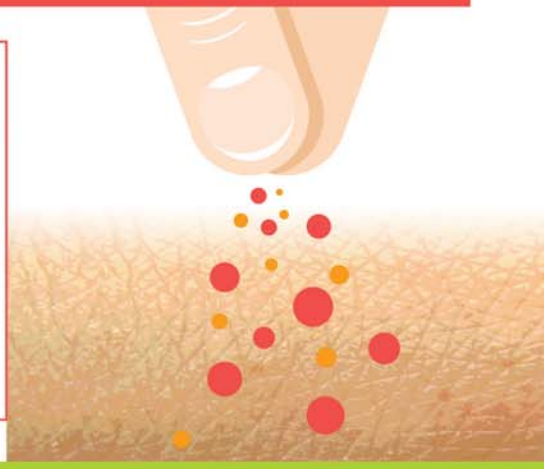
NEW

2007 Certificate Course in Clinical Dermatology 臨床皮膚醫學證書課程

This programme aims to upgrade health care professionals' knowledge and skills in the care of patients with dermatological problems. The Course, jointly organized by the Family Medicine Unit and Division of Dermatology, consists of 10 weekly seminars conducted by to specialists in dermatology between April and June 2007.

Applicants can choose to attend the full Course or individual seminars. Tuition fee for the whole Course is HK$5,000, and for spot admission is HK$700 per session.

Closing date for application: **31st March 2007**



Application forms for the above programmes can be downloaded from our website:

www.hku.hk/fmunit/geriatrics
www.hku.hk/fmunit/psychiatry
www.hku.hk/fmunit/dermatology

For further information, please contact Magdalene Tang, part-time Executive Assistant at 2518 5688 (voice mail) or 2814 7475 (fax) or email to magtang@hku.hk. Address: Family Medicine Unit, 3/F, Ap Lei Chau Clinic, 161 Main Street, Ap Lei Chau, Hong Kong.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				★HKMA Council Meeting 1	2	3
4	★Asian Menopause & Sexual Well Being Survey - Sex, QoL at Menopause and Management 5	★HKMA Newsletter Editorial Meeting 6	★Joint Professional Golf Tournament 2007 7	★Certificate Course on Gynaecology ★HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2007 (III) - Overactive Bladder 8	9	★HKMA Refresher Course for Health Care Providers 2006/2007 (VII) - Radiological Investigations and Interventions 10
★HKMA Structured CME Programme Year 06/07 (XII)-Clinical Oncology & Cardiothoracic Surgery 11	12	13	14	★Certificate Course on Gynaecology ★Clinical Pathological Conference 15	16	17
★Practical Issues on Managing Diabetes 18	19	20	★Certificate Course on Gynaecology 21	22	23	24
★Hypertension and Diabetics Awareness Program ★HKMA Structured CME Programme Year 06/07 (XII) - Traditional Chinese Medicine 25	26	★健康服務助理員訓練課程 (Code no. TC-HCA-0107) ★Clinical Nurse Specialist Group Evening Forum "Managing Urinary Incontinence - Chinese & Western Approaches" (Code no. SCNSG-07-02) 27	★Enhancement of Bone Health with Milk Basic Protein 28	★Certificate Course on Gynaecology 29	★健康服務助理員訓練課程 (Code no. TC-HCA-0107) 30	31

Medical Diary of March

Date / Time	Function	Enquiry / Remarks
1 THU 8:00 pm	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Christine WONG Tel: 2527 8285
5 MON 7:00 pm - 10:00 pm	**Asian Menopause & Sexual Well Being Survey - Sex, QoL at Menopause and Management** Organised by: The Obstetrical and Gynaecological Society of Hong Kong Chairman: Dr. S.K. LAM Speaker: Dr. Hans REKERS & Dr. Elizabeth FARRELL # Crystal Ballroom B, Basement 3, Holiday Inn Golden Mile, Tsimshatsui, Kowloon	Ms. Pansy YU Tel: 2833 6380 1 CME Point (HKCOG, HKCFP, MCHK)
6 TUE 8:00 pm	**HKMA Newsletter Editorial Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Tammy TAM Tel: 2527 8941
7 WED 12:00 pm	**Joint Professional Golf Tournament 2007** Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG & Dr. L HOU # Jockey Club Kau Sai Chau Public Golf Course, Sai Kung	Ms. Dora HO Tel: 2527 8285
8 THU 7:30 pm - 8:30 pm (15, 21, 29)	**Certificate Course on Gynaecology** Organised by: The Federation of Medical Societies of Hong Kong & The Obstetrical and Gynaecological Society of Hong Kong Chairman: Dr. HUNG Kwan Ngai & Dr. S.K. LAM Speaker: Various # 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Karen CHU Tel: 2527 8898 Fax: 2865 0345
2:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2007 (III) - Overactive Bladder** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Chairman: Dr. T.C. SHIH Speaker: Dr. WONG Wai Sang # HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Nina HUNG Tel: 2861 1979 (Registration fee is required) 1 CME Point
10 SAT 2:30 pm	**HKMA Refresher Course for Health Care Providers 2006/2007 (VII) - Radiological Investigations and Interventions** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Chairman: Dr. T.C. SHIH Speaker: Dr. CHONG Sui Fan Anita # Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
11 SUN 2:00 pm	**HKMA Structured CME Programme Year 06/07 (XII)-Clinical Oncology & Cardiothoracic Surgery** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Multi-function Room, G/F, Block D, Queen Elizabeth Hospital, Kowloon	Miss Nina HUNG Tel: 2861 1979 (Registration Fee is required) 3 CME Points
15 THU 7:00 pm - 8:30 pm	**Clinical Pathological Conference** Organised by: The Hong Kong Society for Colposcopy and Cervical Pathology & Department of O&G, Prince of Wales Hospital Chairman: Dr. YIM So Fan Speaker: Dr. May YU & Dr. Nelson SIU # 1/F, Allan Chang Seminar Room, Department of O&G, Prince of Wales Hospital, Shatin	Ms. Phyllis KWOK Fax: 2855 0947
18 SUN 2:00 pm	**Practical Issues on Managing Diabetes** Organised by: The Hong Kong Medical Association Chairman: Dr. C.H. CHOI & Dr. K.L. CHOI Speaker: Various # Lecture Theatre, G/F, Block M, Queen Elizabeth Hospital, Kowloon	Miss Gloria CHEUNG Tel: 2527 8285 (Registration fee is required) 3 CME Points
25 SUN 2:00 pm	**Hypertension and Diabetics Awareness Program** Organised by: The Hong Kong Medical Association Chairman: Dr. C.P. HO Speaker: Various # Hospital Authority Building, 147B Argyle Street, Kowloon	Miss Gloria CHEUNG Tel: 2527 8285 (Open to public)
2:00 pm	**HKMA Structured CME Programme Year 06/07 (XII) - Traditional Chinese Medicine** Organised by: The Hong Kong Medical Association & Kwong Wah Hospital Chairman: Dr. T.C. SHIH Speaker: Dr. CHEUNG Hon Ming # Lecture Theatre, 10/F, Yu Chun Keung Memorial Medical Centre, Kwong Wah Hospital, 25 Waterloo Road, Kowloon	Miss Nina HUNG Tel: 2861 1979 (Registration fee is required) 3 CME Points
27 TUE 6:00 pm - 10:00 pm (30)	**健康服務助理員訓練課程** (Code no. TC-HCA-0107) Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280
6:00 pm to 8:30 pm	**Clinical Nurse Specialist Group Evening Forum "Managing Urinary Incontinence - Chinese & Western Approaches" (Code no. SCNSG-07-02)** Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280
28 WED 7:00 pm - 9:30 pm	**Enhancement of Bone Health with Milk Basic Protein** Organised by: The Obstetrical and Gynaecological Society of Hong Kong Chairman: Dr. S.K. LAM Speaker: Mr. Dosako SHUNICHI # Ballroom, Penthouse, Hotel Miramar, Tsimshatsui, Kowloon	Ms Pansy KO Tel: 2529 8931 1 CME Point (HKCOG)

Courses

18,19/5/2007	**IOF Osteoporosis Diagnosis Course** Organised by: The Osteoporosis Society of Hong Kong, The University of Hong Kong (The Osteoporosis Centre & Research Centre of Heart, Brain, Hormone and Healthy Aging) Chairman: Prof. Annie KUNG # 6/F, Old Wing, The Hong Kong Convention & Exhibition Centre Enquiry: Ms. Cissy SOONG Tel: 2855 4353 Fax: 2855 1701
9,10,11/7/2007	**Definitive Surgical Trauma Care (DSTC) Course** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: http://www.hku.hk/surgery
24,25,26/8/2007	**Advanced Trauma Life Support (ATLS) Student Course** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: http://www.hku.hk/surgery

Calendar of Events

Meetings

19-20/5/2007	**8th Regional Osteoporosis Conference** Organised by: The Osteoporosis Society of Hong Kong & The University of Hong Kong (The Osteoporosis Centre & Research Centre of Heart, Brain, Hormone & Health Aging) Chairman: Prof. Annie KUNG # 6/F, Old Wing, The Hong Kong Convention & Exhibition Center Enquiry: Ms. Cissy SOONG Tel: 2855 4353 Fax: 2855 1701
13-17/06/2007	**The 21st Congress of International Association of Paediatric Dentistry IAPD** Organised by: Hong Kong Society of Paediatric Dentistry # Hong Kong Convention & Exhibition Centre Enquiry: Mr. Daniel CHOK Tel: 2871 8896 Fax: 2871 8898 Email: info@iapd2007.com Website: http://www.iapd2007.com
12/7/2007	**The 1st Nursing Forum** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong; American College of Surgeons, Hong Kong Chapter & Department of Nursing Studies, Li Ka Shing Faculty of Medicine, The University of Hong Kong # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 / 2855 4886 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery
12-14/7/2007	**The 50th Hong Kong Surgical Forum** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong & American College of Surgeons, Hong Kong Chapter # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 / 2855 4886 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery
17-18/11/2007	**Annual Scientific Meeting in Anaesthesiology 2007 - Expanding the Boundaries** Organised by: The Hong Kong College of Anaesthesiology & The Society of Anaesthetists of Hong Kong # Hong Kong Convention and Exhibition Centre, Wanchai, Hong Kong Enquiry: Secretariat (CMPMedica Pacific Limited) Tel: 2559 5888 Fax: 2559 6910 Email: meeting.hk@asia.cmpmedica.com Website: www.hkca.edu.hk/asm2007.htm

Federation News

The new FMSHK Executive Committee

We are pleased to announce the new Office Bearers for 2006-2007:

President:	**Dr Dawson T.S. Fong**
1st Vice President:	**Dr Chan Chi Kuen**
2nd Vice President:	**Dr Susanna S.C. Lo**
Honorary Secretary:	**Dr Raymond S.K. Lo**
Deputy Hon. Secretary:	**Dr Chan Sai Kwing**
Honorary Treasurer:	**Mr. Nelson L.C. Lam**
Deputy Hon. Treasurer:	**Mr Benjamin C.M. Lee**

Executive Committee Members

Dr Godfrey CF Chan
Dr James CS Chim
Dr Ho Chung Ping
Dr Hung Kwan Ngai
Dr Walter WK King
Dr Albert MP Lee
Dr Dominic FH Li
Ms. Manbo BL Man
Dr Man Chi Wai
Dr Mok Chun On
Mr Peter YY To

The Federation's Annual Dinner 2006

Photographs: Wonderful photographs from our Annual Dinner 2006 are now available for ordering! Please visit our gallery to view and choose http://www.fmshk.org/dinner2006

Questionnaire: Your valuable feedback is important to us for future improvement of the Annual Dinner. Please fill in the questionnaire at http://www.fmshk.org/questionnaire

Please contact the Secretariat, Karen Chu at 2821 3515 or email karen.chu@fmshk.org for enquiries and assistance.

Society News

News from Member Societies:

The Hong Kong Society of Community Medicine
Dr Ronald Lam has been appointed as the society's council representative effective from 1st January 2007.

Hong Kong Society of Palliative Medicine
New office-bearers for the year 2006-2007 are as follows: Chairman: Dr. WONG Kam Hung, Vice Chairman: Dr YEUNG Mei Wan, Rebecca & Dr. Anne B THORSEN, Hon. Secretary: Dr KWOK Oi Ling, Annie, Hon. Treasurer: Dr YUEN Kwok Keung

CERTIFICATE COURSE FOR HEALTHCARE PROFESSIONALS

Certificate Course on Gynaecology

婦 科 證 書 課 程

(Course No. C115)

FOR THE FAVOUR OF POSTING

Jointly organized by

The Federation of Medical Societies of Hong Kong
香 港 醫 學 組 織 聯 會
&
The Obstetrical and Gynaecological Society of Hong Kong
香 港 婦 產 科 學 會

Objective: To learn the recent advances in gynaecology especially on the use of new technology in treating gynaecological diseases

DATE	TOPIC	SPEAKER
8 March 2007 (Thur)	Contraception: Current Trend and Update 避孕新趨勢	Dr Grace Wong 王靜妍醫生
15 March 2007 (Thur)	Update on Urogynaecology 泌尿婦科日日新	Dr KS Wong 黃建新醫生 Ms B Fung 物理治療師馮潔玉小姐
21 March 2007 (Wed)	Update on Infertility and Assisted Reproductive Technology 不育及生殖科技新知	Dr Ernest Ng 吳鴻裕醫生
29 March 2007 (Thur)	Cervical Smear and Colposcopy 宮頸抹片及陰道鏡	Dr SK Lam 林兆強醫生
12 April 2007 (Thur)	Common Gynaecological Cancer and Their Treatment 常見婦科癌病及治療	Dr SF Yim 嚴素芬醫生
19 April 2007 (Thur)	Common Menstrual Problems and Their Management 常見月經問題及療法	Dr PM Yuen 阮邦武醫生

Date : March 8, 15, 21, 29 and April 12, 19, 2007
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Course Fee : HK$960 (6 Sessions)
Language : Cantonese (Supplemented with English)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of the Federation of Medical Societies of Hong Kong
Tel. : 2527 8898 **Fax** : 2865 0345 **Email** : info@fmshk.org

CME/CPE Accreditation applied for

For downloading the application form, please refer to our website: http://www.fmshk.org

A NEW BEGINNING IN PAH THERAPY

A New, Oral Agent Proven Effective and Well-tolerated for Use in Symptomatic Patients With Pulmonary Arterial Hypertension (PAH)[1]

REVATIO is indicated for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise ability and mean pulmonary arterial pressure. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Sildenafil potentiates the hypotensive effects of nitrates; therefore the concomitant use of REVATIO with nitrates is contraindicated.

Reference: 1. Galiè N, Ghofrani HA, et al. Sildenafil citrate therapy for pulmonary arterial hypertension, *N Engl J Med*. 2005;353:2148-57. **Please see full prescribing information.**

NEW

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REVATIO ABBREVIATED PACKAGE INSERT **TRADE NAME:** Revatio **PRESENTATION:** Revatio oral film-coated tablet contains 20 mg of sildenafil (as citrate). **INDICATIONS:** Treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. **DOSAGE:** Taken with or without food. Adults ≥18 years old and elderly ≥ 65 years old: 20 mg three times a day; impaired renal function and impaired hepatic function (Child-Pugh class A and B): 20 mg twice daily only if therapy is not well-tolerated. Not recommended in children and adolescents < 18 years or co-administer with other treatments for pulmonary arterial hypertension (e.g. bosentan, epoprostenol, iloprost); Dose adjustment after careful benefit-risk assessment: concomitant with medium potency CYP3A4 inhibitors e.g. erythromycin or saquinavir: 20 mg twice daily; concomitant with clarithromycin, telithromycin or nefazodone: 20 mg once daily. Dose adjustments may be required if co-administered with CYP3A4 inducers. A gradual dose reduction and intensified monitoring during the discontinuation period should be considered if withdrawal. **CONTRAINDICATIONS:** Hypersensitivity to sildenafil or any excipients; concomitant use with nitrates, nitric oxide donors (such as amyl nitrite), nitrates in any form or potent CYP3A4 inhibitors (eg. ketoconazole, itraconazole, ritonavir); severe hepatic impairment (Child-Pugh class C), recent history of stroke or myocardial infarction, severe hypotension (blood pressure < 90/50 mmHg) at initiation. **WARNINGS & PRECAUTIONS:** Patients had risk factors for non-arteritic anterior ischemic optic neuropathy (NAION); underlying conditions adversely affected by vasodilatory effects of sildenafil e.g. hypotension, fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction; patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or predispose to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia); patients with increased risk of bleeding e.g using a Vitamin K antagonist, patients with PAH secondary to connective tissue disease. Patients with signs of pulmonary oedema or any symptoms associated with veno-occlusive disease; patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Patients should be aware of dizziness and altered vision as reported as side effects of Revatio, caution should be exercise before driving or operating machinery. **INTERACTIONS:** CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers; CYP3A4 inducers, e.g. bosentan, carbamazepine, phenytoin, phenobarbital, St John's wort and rifampicine; CYP3A4 inhibitors, e.g. ritonavir, ketoconazole, itraconazole, cimetidine, clarithromycin, telithromycin, nefazodone, saquinavir, erythromycin, grapefruit juice; nicorandil; alpha-blocker; nitrates; nitric oxide donors or nitrates in any form. **PREGNANCY AND LACTATION:** Revatio should not be used in pregnant women or breast-feeding mothers unless strictly necessary. **SIDE EFFECTS:** Headache, flushing, dyspepsia, back pain, diarrhoea and limb pain. Myalgia, cough, epistaxis, insomnia, pyrexia, influenza, visual disturbance. **Reference:** HK PI (Feb 2006). **Date of preparation:** Jun 2006. **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

REV07001P