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# A Pilot Study of Intravenous Urapidil, α1-Adrenergic Blockade in the Treatment of Severe Congestive Heart Failure

GUO-GAN WANG,[1] HAO WANG,[2] WENQIAO XU,[2] JUN ZHU,[1] YOUCHEN SONG[1] AND KAM-SANG WOO[3]

From [1]Department of Cardiology, Department of Emergency, Fuwai Heart Hospital; Cardiovascular Institute, Chinese Academy of Medical Sciences, Peking Union of Medical College; [2]Department of Echocardiography, Fuwai Heart Hospital, Beijing, China; [3]Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR

**WANG ET AL.:** ***A Pilot Study of Intravenous Urapidil, α1-Adrenergic Blockade in the Treatment of Severe Congestive Heart Failure. Objective:*** *The aim of this study was to evaluate the efficacy and tolerability of small dose urapidil in the treatment of patients with severe congestive heart failure.* ***Methods:*** *Thirty patients with severe (NYHA class IV) congestive heart failure (male 16, female 14; mean age 55.3 ± 15.6 years) were randomly assigned to open-labeled treatment with urapidil (Group A, 15 patients) or nitroglycerin (Group B, 15 patients). Five patients had old myocardial infarction, 2 had essential hypertension, 22 idiopathic dilated cardiomyopathy, and one had peripartum cardiomyopathy. Both groups were comparable in respects of age, heart rate and blood pressure. Urapidil (100 μg/min) or nitroglycerin (20 μg/min) was administered intravenously for 24 hours in addition to conventional treatment of heart failure (oxygen, diuretic and digitalis). Heart rate, blood pressure, blood gas and echocardiography were measured before and after the treatment.* ***Results:*** *After treatment, relative changes of heart rate, diastolic blood pressure and blood gas compared with baseline were not significantly different in both groups. However, systolic blood pressure at 2 hours and 6 hours after treatment were lower in groups B (nitroglycerin) patients. In group A, the left ventricular systolic parameters and stroke volume measured by echocardiography increased significantly compared with baseline, and so were left ventricular ejection fraction and maximum flow velocity of aortic valve. In comparison, in group B, only left ventricular ejection fraction increased and flow accelerate time of E wave prolonged significantly.* ***Conclusion:*** *Small dose intravenous urapidil is a potentially useful agent in the management of severe congestive heart failure, demonstrating a significant improvement in cardiac systolic function and good tolerability. (J HK Coll Cardiol 2005;13:54-58)*

*Heart failure; Urapidil*

**摘要**

**目的：**評價小劑量烏拉地爾治療嚴重充血性心力衰竭療效和安全性。**方法：**嚴重充血性心力衰竭（紐約心功能分級，IV級）患者30例（男性16例，女性4例），平均年齡55.3±15.6歲。病因包括：冠心病陳舊性心肌梗死5例、高血壓病2例、擴張性心肌病22例、圍產期心肌病1例。入院後採用隨機方法分爲烏拉地爾組（A組）15例，硝酸甘油組（B 組）15 例。兩組間年齡、心率、血壓無顯著性差異。兩組患者在常規心衰治療基礎上（如吸氧、利尿劑、洋地黃治療），分別靜脈使用A組烏拉地爾（100 μg /min）或B組（硝酸甘油20 μg/min）24小時。分別檢查用藥前、用藥後心率、血壓、血氣分析、超聲心動圖。**結果：**兩組患者用藥後心率、舒張期血壓、血氣分析參數與用藥前比較無顯著性差異。但是，B組（硝酸甘油）患者用藥後2小時、6小時收縮期血壓減低較明顯。A組（烏拉地爾）患者超聲心動圖參數的收縮功能指標SV明顯增大、EF%明顯增大、AoVmax明顯增快。B組患者的收縮功能指標僅EF%明顯增大，舒張功能指標中E dct明顯延長。**結論：**小劑量持續靜脈泵入烏拉地爾可有效用於充血性心力衰竭治療，能明顯改善患者心臟收縮功能，同時患者耐受性較好。

關鍵詞：心力衰竭　烏拉地爾

Address for reprints: Dr. Guo-Gan Wang
Department of Cardiology, Department of Emergency, Fuwai Heart Hospital, No. 167 Beilishi Avenue, Beijing 100037, P.R. China
Email: wangguog@hotmail.com

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## Introduction

Urapidil can, as an α1-adrenergic receptor blockade, dilate peripheral small artery and reduce the resistance of peripheral vessel by both blocking postsynaptic α1-adrenergic receptor and central mechanisms.[1-3] Preliminary data suggest it has favourable blood pressure-lowering effects in treatment of hypertensive emergencies.[3-5] Some studies suggested urapidil could be used to treat congestive heart failure, because it can increase cardiac index and reduce peripheral resistance and mean pulmonary artery wedge pressure without reflex tachycardia.[2,6-9] This special pharmacological property may be particularly appealing in heart failure therapy, as use of many regimens, including vasodilators, are often limited by the reflex tachycardia.

The aim of this study was to evaluate the efficacy and tolerability of small dose urapidil for the treatment of patients with severe congestive heart failure.

## Patients and Methods

Thirty patients admitted into the Fuwai Heart Hospital in Beijing with severe (NYHA class IV) congestive heart failure were enrolled. Fourteen were female and 16 were male, their mean age were 55.3± 15.6 years (range 14-76 years). The aetiology of the congestive cardiac failure were old myocardial infarction (in 5 patients), essential hypertension (in 2 patients), idiopathic dilated cardiomyopathy (in 22 patients) and peripartum cardiomyopathy (in 1 patient).

*Inclusion criteria* were as follows: Need for intensive care treatment for acute left heart decompensation (orthopnea with clinical and radiological signs of severe pulmonary congestion) in emergency ward and intensive care unit. Patient with acute myocardial ischaemia on the basis of chest pain, ECG and enzyme kinetics (troponins T and creatine kinase) was excluded.

*Study Protocol:* Thirty patients were randomly assigned to open-labeled urapidil treatment (Group A, 15 patients) or nitroglycerin (Group B, 15 patients). Intravenous urapidil, (Germany Byk Gulden Corporation) 100 μg/min, was administered by infusion pump for 24 hours in group A, and intravenous nitroglycerin 20 μg/min was given by infusion pump for 24 hours in group B. Conventional treatments of heart failure (including inhaled oxygen, diuretic and digitalis) were continued, except that other vasodilators and angiotensin converting enzyme inhibitor which were stopped temporarily. Patients were monitored closely, and their blood pressures and heart rate profiles at baseline and hourly intervals after starting treatment, as well as clinical features including severity of dyspnoea symptom and echocardiographic profiles at baseline and 24 hours after treatment in the 2 groups were compared. Any adverse reactions during the infusion treatment were recorded.

Echocardiography parameters include: left ventricular diastolic end diameter (LVEDd), left ventricular stroke volume (SV), and left ventricular eject fraction (EF%) measured by 2D-guided M-Mode, maximum flow velocity of aortic valve (AoVmax), flow accelerate time of aortic valve (AoVact) and flow shift parameters measured by standard Doppler echocardiographic technique.

*Statistical analysis:* Changes in blood pressure and echocardiographic parameters were tested for significance using the Student's t test for paired samples. A probability level of $P<0.05$ was considered significant for the study.

## Results

The 2 groups were comparable in the baseline clinical and echocardiographic diameters (Table 1).

*Changes in clinical parameters*: There were no significant changes in heart rate and diastolic blood pressure after treatment in both groups. However, the systolic blood pressure at 2 hours and 6 hours after treatment were significantly lower in group B but not in group A patients (see Figure 1).

Some patients in both groups receive inotrope

**Table 1. Clinical features of 2 groups at baseline**

| | Urapidil group (n=15) | Nitroglycemia group (n=15) | p-value |
|---|---|---|---|
| Age (year) | 55.8±16.7 | 54.8±14.6 | NS |
| SBP (mm) | 115.6±12.3 | 114.1±18.9 | NS |
| DBP (mm) | 70.1±8.6 | 69.8±8.5 | NS |
| Heart Rate (beats/min) | 89.2±9.1 | 89.4±8.9 | NS |
| CAD | 3 | 2 | NS |
| HHD | 1 | 1 | NS |
| DCM | 11 | 11 | NS |
| LVEF (%) | 22.1±3.6 | 25.6±2.4 | NS |

CAD: coronary artery disease; DCM: dilated cardiomyopathy; DBP: diastolic blood pressure; HHD: hypertensive heart disease; LVEF: left ventricular ejection fraction; NS: not significant; SBP: systolic blood pressure

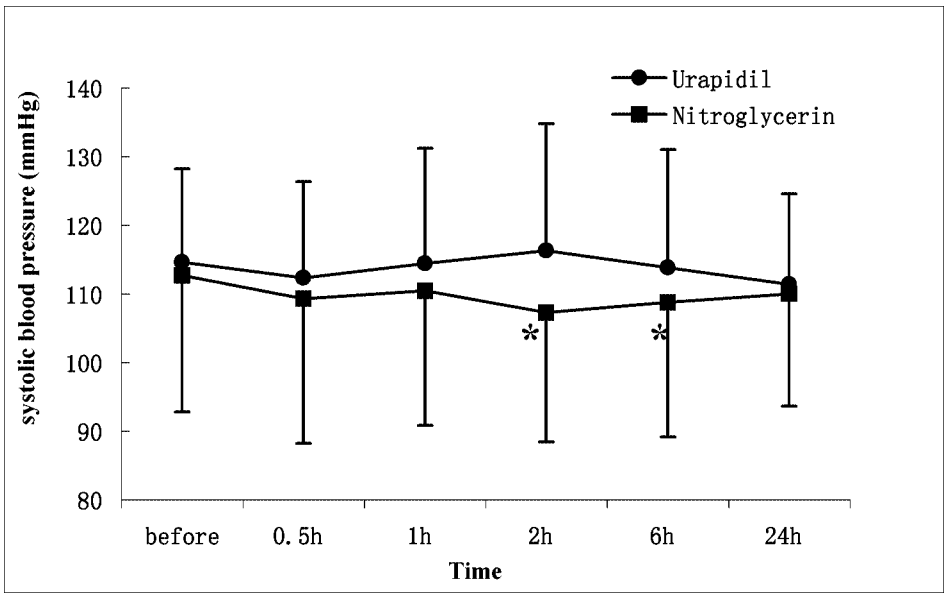


**Figure 1.** *Changes in systolic blood pressure in both groups. The systolic blood pressures at 2h and 6h after treatment were lower significantly in group B (nitroglycerin) patients but not in group A (urapidil) patients. *P<0.05 vs before treatment.*

treatment (8 dopamine, 5 milrinone, 3 amrinoone in group A; and 8 dopamine, 7 milrinone, 2 amrinoone in group B respectively) in addition to digitalis after 24 hours admission.

Clinical symptoms improved after treatment in both patient groups. There were no adverse drug reaction present, with no dizziness, palpitation, nor nausea, but one group B patient developed transient atrial fibrillation.

During hospital, there are two patients occurring atrial fibrillation and one patient with multifocal premature ventricular complexes in group A. However, in both groups, no any patient received mechanical ventilation and died in hospital. There are no significant different in duration of ICU and in hospital between group A and group B (7.0±2.5, 8.3±3.5, p=0.18; 14.3±7.8, 17.7±6.6, p=0.08, respectively).

*Changes in cardiac function parameters:* In group A, the stroke volume increased significantly compared with baseline (57.7 vs 70.9 ml, p<0.01),

and so were ejection fraction and AoVmax (22.1% vs 29.7%, p<0.01 and 0.89 m/s vs 1.04 m/s, p<0.05 respectively) (see table). In group B, only ejection fraction increased significantly (25.6% vs 29.7%, p<0.01), while flow decelerate of E wave (E dct) were significantly prolonged (108.9 ms vs 125.0 ms, p<0.01) (Table 2).

*Blood gas parameters:* There were no significant changes in blood gas parameters after treatment in the two groups.

## Discussion

It is well known that low cardiac output, excessive blood pooling in venous circulation and increase peripheral vascular resistance are the principal haemodynamic alterations in congestive heart failure. In this process, neurohumoral activation (autonomic nervous system and renin-angiotensin-aldosterone systems) takes place,[6] resulting in increase in heart rate and systemic vascular resistance, reduction in tissue purfusion, retention of sodium and water and cardiac failure deterioration.

During past decades, vasodilators have been developed, which have been proven a major advance in the treatment of heart failure, in decreasing the preload and afterload of the heart, with subsequent curative effect. Studies have documented that they were well tolerated and effective in improving heart failure symptoms.[6,9]

Nitroglycerin can, as predominantly a venodilator, reduce blood volume return to heart leading to a decrease preload of heart, but relatively little effect on resistance of peripheral vessel and cardiac output.[6]

This study results show that there were no improvement in LVEDd and SV 24 hours after infusion nitroglycerin, but an increase in EF% (16%) which however was less than in group A (33.8%).

Urapidil is a new antihypertensive agent with unique properties initially designed for the treatment

**Table 2. Changes in echocardiographic parameters in both groups**

| | Urapidil | | | Nitroglycerin | | |
|---|---|---|---|---|---|---|
| | Before | After | P | Before | After | P |
| LVEDd (cm) | 7.2±0.8 | 7.0±0.9 | NS | 7.0±0.8 | 6.9±0.9 | NS |
| FS% | 14.5±1.9 | 14.2±1.8 | NS | 14.0±1.9 | 13.0±1.8 | NS |
| EF% | 22.1±3.6 | 29.7±4.1 | <0.01 | 25.6±2.4 | 29.7±2.5 | <0.01 |
| SV (ml) | 57.7±8.7 | 70.9±7.8 | <0.01 | 58.7±8.9 | 65.3±8.8 | NS |
| AoVmax (m/s) | 0.89±0.09 | 1.04±0.07 | <0.05 | 0.91±0.10 | 0.9±0.11 | NS |
| AoVact (ms) | 84.5±8.2 | 84.3±7.9 | NS | 78.8±8.6 | 84.7±8.1 | NS |
| E act (ms) | 62.3±9.1 | 70.4±8.9 | NS | 69.8±8.9 | 69.3±7.9 | NS |
| E dct (ms) | 118.7±11.2 | 124.2±12.1 | NS | 108.9±9.2 | 125.0±7.9 | <0.01 |
| E et (ms) | 181.6±13.1 | 193.9±14.2 | NS | 178.7±0.1 | 194.8±26.6 | NS |
| TVI | 9.8±1.6 | 9.4±1.5 | NS | 10.6±1.9 | 9.8±1.8 | NS |
| VmaxE (m/s) | 0.87±0.16 | 0.81±0.19 | NS | 0.84±0.18 | 0.82±0.17 | NS |
| VmaxA (m/s) | 0.28±0.18 | 0.32±0.20 | NS | 0.49±0.21 | 0.62±0.22 | NS |
| E/A | 3.4±0.9 | 3.0±0.8 | NS | 1.6±0.8 | 1.6±0.7 | NS |

LVEDd: left ventricular diastolic end diameter, FS%: percentage of fractional shortening, EF%: left ventricular eject fraction, SV: left ventricular stroke volume, AoVmax: max flow velocity of aortic valve, AoVact: flow accelerate time of aortic valve, E act: flow accelerate time of E wave, E dct: flow decelerate time of E wave, E et: flow time of E wave, TVI: integral of tricuspid valve flow, VmaxE: max flow velocity of E wave, VmaxA: max flow velocity of A wave, E/A: ratio of E wave and A wave.

* Expressed as mean ± SD

of hypertension.[3-5] It decreases peripheral vascular resistance by postsynaptic alpha l-blockade, reduction of the central sympathetic tone and inhibition of the pressor baroreceptor reflexes.[1-4] These result in reduction of peripheral vessel resistance, afterload and elevation in cardiac output.[1-4] In addition, some data suggest urapidil therapy and independent of nitric oxide involvement, decreases high circulating levels of endothelin within hours and restore physiological balance across pulmonary, coronary, and peripheral vascular beds,[10] without affecting the sodium excretory capacity of kidney.[11]

In this regard, after urapidil infusion, among the cardiac systolic indices, SV, AoVmax and EF% in particular increased significantly compared to baseline, documenting an improvement in pump function of the heart.

Some previous literature proposed congestive heart failure be treated by continuous infusion of urapidil following a bolus dose.[1-3,7,8] However, a bolus dosage of intravenous urapidil given within a short time could cause hypotension and even shock, as the blood pressure is already usually lower in patients with congestion heart failure. There were no hypotension occurring using a small dosage (100 μg/min) of urapidil by continuous infusion for 24 hour without a bolus dose in the present study.

In addition to its peripheral effects, urapidil could reduce central sympathetic nervous activity via stimulation of serotoninergic 5-hydroxytryptamine 1A receptors in medulla oblongata and affect the baroreceptor reflex, which may explain the lack of reflex tachycardia. Based on these properties, urapidil may have some advantages over other agents used in acute decompensated heart failure. In this context, specifically urapidil can be used to treat congestive heart failure from ischaemia heart disease in particular,[4,7] as well as in hypertensive and idiopathic dilated cardiomyopathy, as it can avoid the potential risk of cardiac ischaemia due to reflex heart rate increase.

## Conclusion

Small dose continuous intravenous urapidil infusion is a potentially useful agent in the management of severe congestive heart failure, with significant improvement in cardiac systolic function and good tolerability.

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# Tachycardia Amongst Subjects Recovering from Severe Acute Respiratory Syndrome (SARS): A Prospective Case Study

SUET-TING LAU,[1] WAI-CHO YU,[1] NGAI-SHING MOK,[1] PING-TIM TSUI,[1] WING-LOK TONG,[1] STELLA WAI-CHEE CHENG[2]

From [1]Department of Medicine & Geriatrics; [2]Occupational Therapy Department, Princess Margaret Hospital, Lai Chi Kok, Hong Kong SAR

**LAU ET AL.:** ***Tachycardia Amongst Subjects Recovering from Severe Acute Respiratory Syndrome (SARS): A Prospective Case Study. Background:*** *SARS is a new infection in humans with unknown medium or long-term complication. Palpitation in the form of tachycardia is common amongst patients recovering from SARS. We studied the extent and possible cause of tachycardia in these patients.* ***Methods:*** *Prospective cross-sectional case series of patients treated in Princess Margaret Hospital in Hong Kong recovering from SARS who had resting heart rate of more than 90 beats per minute (BPM) at follow up about 2 months from onset of illness was recruited for assessment of heart rate and rhythm, cardiac function, pulmonary function, laboratory tests, Quality of Life score and Functional assessment. Patients were followed up in the out-patient clinic for at least 1 year after discharge.* ***Results:*** *Fifteen out of 100 consecutive patients were eligible for study. Median mean heart rate was 82 BPM (range 70-91) with maximum heart rate ranging from 114 to 163 BPM. Sinus tachycardia was recorded only in daytime. Signal average ECG, heart rate variability, and echocardiography were normal. Two patients had significantly impaired spirometic indices while all but one had normal diffusion capacity study. Mean haemoglobin level was 13.4 gm/l (10.6-14.9). Troponin I, thyroid function, arterial blood gases, C reactive protein and liver function tests were normal. Quality of Life (QOL) score was low especially in the psychological well being domain. Monitored Functional Task Evaluation (MFTE) score demonstrated mild functional difficulties in 10 patients (score17.6-19.7). No symptom of palpitation was present at follow up after 1 year.* ***Conclusion:*** *No significant arrhythmia or cardiac abnormality was identified. Sinus tachycardia on exertion in patients recovering from SARS is possibly attributed to physical deconditioning and contributed by psychological impairment. (J HK Coll Cardiol 2005;13:59-67)*

*Severe Acute Respiratory Syndrome, Tachycardia*

**摘要**

**背景：**嚴重急性呼吸系統綜合症（SARS）是人類一種新的傳染性疾病，它中期及長期的併發症不明。SARS痊癒病人往往會出現由於心動過速而產生的心悸。我們研究這些病人產生心動過速的可能原因和程度。**方法：**採用前瞻性病例跟進研究，收集在香港瑪嘉烈醫院接受治療的SARS的病人資料，他們發病後二月的靜息心率超過每分鐘90次。評價他們的心率和心律、心功能、肺功能、實驗室檢查、生活質量評分和功能評價。這些病人在出院後在門診治療接受一年以上的隨訪。**結果：**在100名續貫病例中共有15名適合研究。中位心率爲每分鐘82次（70-91次），最大心率從每分鐘114次至163次。僅在白天記錄到竇性心動過速。平均心電圖信號，心率的可變度、和超聲心動圖均是正常的。有二位病人出現了明顯的肺活量損害，而其中一位未達到了正常彌散容積。平均血紅蛋白值爲13.4 gm/l（10.6-14.9）。肌鈣蛋白、甲狀腺功能、動脈血氣、C反應蛋白和肝功能均正常。在那些心理上有陰影的病人，生活質量評分分值就很低。在10位病人中，監控功能性任務評估顯示出輕微功能性困難（分值爲17.6-19.7）。一年後病人沒有出現心悸的症狀。**結論：**在這些病人中沒有發現明顯的心律失常或心功能異常。竇性心動過速在SARS痊癒病人中的出現，原因可能在於身體的去適應和心理的損害。

關鍵詞：嚴重急性呼吸系統綜合症　心動過速

Address for reprints: Dr. Suet-Ting Lau
Department of Medicine & Geriatrics, Princess Margaret Hospital, Lai Chi Kok, Kowloon, Hong Kong

Tel: (852) 2990 3581; Fax: (852) 2990 3148

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## Introduction

SARS is a severe, readily transmissible disease caused by a novel coronavirus.[1,2] It emerged in mid-November 2002 in Mainland China and Hong Kong became affected in March 2003.[3] By late June 2003 there were 8,439 cases worldwide and 1,755 cases in Hong Kong, the latter being one of the hardest hit areas.[4] While the presenting features and acute clinical course has been well studied,[5-8] whether there are medium to long-term complications remain unknown. Princess Margaret Hospital (PMH) had managed 585 confirmed cases up to end of June, 2003. At follow up visits patients complained of palpitation in the form of fast heart beat and a resting rate of over 90 beats per minute (BPM) was not uncommon among them. Such patients may experience palpitation at rest and this became marked during mild exertion, often with associated shortness of breath. 12 lead ECG showed sinus tachycardia. Possible causes are deconditioning,[9] impaired pulmonary function, impaired cardiac function, cardiac arrhythmia, thyroid dysfunction, anaemia, autonomic dysfunction[10,11] and anxiety state. This case study aims at finding out the extent of tachycardia, the likely explanation(s) for the tachycardia and the condition after 1 year.

## Methods

This is a prospective cross-sectional case series study involving SARS patients treated in PMH in Hong Kong – a district hospital designated to treat SARS patients during the outbreak in March 2003. All patients were offered pulmonary function tests including spirometric and diffusion studies at follow up around 2 months from onset of illness. Blood pressure and resting heart rate after sitting for 10 minutes were checked before the tests. Subjects with sitting heart rate ≥90 BPM out of the first 100 consecutive patients were recruited into the study. Written informed consent was obtained.

The following laboratory investigations were done at recruitment: Arterial blood gases (ABG), complete blood picture (CBP), erythrocyte sedimentation rate (ESR), liver function tests (LFT), free-thyroxin (FT4), thyroid stimulating hormone (TSH), lactate dehydrogenase (LDH), creatine kinase (CK), troponin-I, C-reactive protein (CRP).

Quality of life (QOL) assessment and functional assessment were done at the same hospital visit. For QOL assessment, we employed World Health Organization (WHO) QOL-BREF[12] that is an abbreviated version of the WHO QOL-100. The questionnaire has been translated into Chinese and validated locally (WHO QOL-BREF Hong Kong-unpublished data) and it encompasses 4 life domains including physical health, psychological well being, social interaction and environmental aspects. The tool for functional assessment was the Monitored Functional Task Evaluation (MFTE)[13] developed in Hong Kong and adopted by the Occupational Therapists Committee in Hospital Authority Hong Kong for the SARS Rehabilitation Programme. The QOL questionnaire and METE are attached as Appendix.

The following cardiac investigations were completed within 1 week of recruitment: 12-lead ECG at rest, signal average ECG (SAECG), Holter monitoring with heart rate variabililty (HRV) using time domain analysis, and echocardiography including M-mode, 2-D and colour Doppler studies.

Patients were offered the Rehabilitation programme on voluntary basis and regularly followed up at 3 month intervals for more than 1 year after discharge.

The Ethics Committee of the Kowloon West Cluster of the Hong Kong Hospital Authority approved the study.

## Results

Fifteen consecutive patients complied with the inclusion criteria were recruited amongst the initial 100 patients attending the lung function test. There were 8 male and 7 female patients, aged from 25 to 62 (mean 34.4). All patients had at least 4-fold rise (<25/200-1600) in SARS-coronavirus antibody titre. The resting 12-lead ECGs showed a sinus heart rate ranged 90 to

109 BPM. They were normal, except in patient 4 who had a partial right bundle-branch block. Holter monitoring demonstrated a mean heart rate of 82.3 BPM (range 70-91, SD 5.05) with maximum heart rates of 114-163 BPM. Eleven patients had sinus tachycardia of more than 130 BPM (Table 1). Overall heart rate more than 100 BPM was observed during the day time (9:00am to 9:00pm) but not at night. No other arrhythmia was detected. Heart rate variability using the time domain analysis showed that the Standard deviation of all normal RR interval (SDNN) was normal (SDNN >100 ms in patients <60 years of age and 97 ms in the 62 year old patient) (Table 1). SAECG was within normal criteria in all subjects. Echocardiography revealed no abnormality apart from the 62-year-old patient who had mild diastolic dysfunction.

Eight patients had normal spirometric indices, 5 had mild impairment and 2 had moderate to severe impairment. Carbon monoxide diffusing capacity was normal for all but patient 4 who also had mild spirometric and restrictive defect (Table 2).

Chest X-ray at follow-up was normal in 5 patients and abnormal in 10. The latter group included the 2 patients with moderate to severe spirometric impairment and some, but not all, patients with mild spirometric impairment.

Mean haemoglobin level was 13.4 gm/l (range 10.6-14.9). White cell counts, ESR, LDH, CK, troponin I, thyroid function tests, arterial blood gases, C-reactive protein and LFTs were normal. The length of hospital stay varied from 18 to 54 days and the period after discharge varied from 14 to 51 days (Table 3). Most patients also had complications that could account for a protracted course of illness and impaired recovery (Table 3). No specific complication was identified in Patient 11 who was aged 62, the eldest patient in this cohort.

The QOL domain score was impaired (score <75) in 11/15 in physical health, 13/15 in psychological well being, 9/15 in social interaction and 11/15 in environmental aspects. Severe impairment with a score of ≤50 occurred in six patients in the psychological well

**Table 1. Holter monitoring results**

| | Sex | Age | Min HR | Max HR | Mean HR | HR Variability SDNN (ms, N>100 ms) |
|---|---|---|---|---|---|---|
| 1 | M | 25 | 50 | 141 | 87 | 133 |
| 2 | F | 30 | 46 | 154 | 77 | 181 |
| 3 | F | 25 | 47 | 153 | 84 | 167 |
| 4 | M | 40 | 52 | 136 | 82 | 131 |
| 5 | F | 34 | 61 | 152 | 85 | 104 |
| 6 | F | 28 | 53 | 145 | 91 | 123 |
| 7 | M | 33 | 50 | 137 | 87 | 118 |
| 8 | M | 49 | 51 | 142 | 83 | 137 |
| 9 | F | 26 | 49 | 129 | 77 | 135 |
| 10 | F | 39 | 51 | 116 | 79 | 103 |
| 11 | M | 62 | 53 | 114 | 70 | 97 |
| 12 | M | 36 | 57 | 123 | 83 | 111 |
| 13 | F | 25 | 55 | 163 | 85 | 147 |
| 14 | M | 26 | 54 | 147 | 83 | 122 |
| 15 | M | 47 | 50 | 135 | 82 | 140 |

Age = Age in years; Min HR = Minimum heart rate beats per minute; Max HR = Maximum heart rate beats per minute; SDNN = Standard deviation mean RR interval

**Table 2. Pulmonary function testing**

| | FVC FEV | Flow rates | Lung volume | DLCO | Interpretation |
|---|---|---|---|---|---|
| 1 | N | Low | N | N | Normal |
| 2 | N | N | N | N | Normal |
| 3 | Low | Low | Decreased | N | Restrictive moderate |
| 4 | Low | N | Increased | N | Obstructive very mild |
| 5 | Low | Low | N | N | Restrictive mild |
| 6 | Low | Low | Low | N | Restrictive severe |
| 7 | Low | Low | Low | Low | Restrictive mild |
| 8 | N | N | Increased | N | Normal |
| 9 | Low | Low | N | N | Normal |
| 10 | N | N | Increased | N | Normal |
| 11 | N | Low | Increased | N | Obstructive mild |
| 12 | N | N | N | N | Normal |
| 13 | N | N | N | | Normal |
| 14 | Low | Low | Decreased | N | Restrictive very mild |
| 15 | N | N | N | N | Normal |

FVC = Force Vital Capacity; FEC = Force Expiratory Volume; DLCO = Diffusing Capacity for Carbon Monoxide

**Table 3. Other factors**

| | CXR finding | Hb | LOS | Discharge to PFT | Complication |
|---|---|---|---|---|---|
| 1 | Mottling RLZ | 13 | 35 | 31 | AD |
| 2 | N | 12.8 | 25 | 36 | AD |
| 3 | Bilat shadowing | 13.3 | 54 | 21 | SP, CI |
| 4 | N | 14.5 | 37 | 14 | Pne |
| 5 | Bilat lower zone hazziness | 12.8 | 30 | 18 | ICU |
| 6 | Bilat lower zone hazziness | 12.9 | 39 | 23 | ICU |
| 7 | Bilat middle zone hazziness | 14.1 | 35 | 21 | ICU |
| 8 | Mild hazziness RLZ, LMZ | 13.1 | 21 | 51 | AD |
| 9 | N | 13.9 | 24 | 33 | AD |
| 10 | Bilat lower zone hazziness | 10.6 | 31 | 18 | UTI |
| 11 | N | 12.6 | 18 | 34 | |
| 12 | Bilat diffuse hazziness | 14.6 | 21 | 45 | CI |
| 13 | N | 13.6 | 21 | 21 | CI |
| 14 | Bilat M&LZ hazziness | 14.9 | 25 | 23 | ITP |
| 15 | Bilat lower zone hazziness | 13.5 | 29 | 29 | ICU |

Hb = Haemoglobin in g/dl; LOS = Length of hospital stay in days; Discharge to PFT = Discharge to day of pulmonary function test in days; ICU = ICU Care; ITP = Idiopathic thrombocytopenic purpura; UTI = Urinary tract infection; CI = Chest infection; AD = Anxiety depression; SP = Steroid psychosis; Pne = Pneumomediastinum and subcutaneous emphysema

being domain. MFTE score was less than 20 (range 17.6 -19.7) in 10 patients indicating the presence of mild functional difficulties (Table 4).

All patients were regularly followed up and no medication that could cause tachycardia was given.

Eleven of the 15 patients joined the rehabilitation programme of the hospital. All patients were followed up for 12 to 20 months after discharge. Patient 9 had a low score in the social relationship score (50), low MFTE score (19.6) and declined rehabilitation. She had anxiety, poor sleep and occasional forceful palpitation and repeated Holter monitoring at the 1 year follow up showed normal finding. The rest of the patients had no symptom of palpitation or dypsnoea at the follow up at 12 to 20 months.

## Discussion

Palpitation at about 2 months after onset of illness raised concern for both the clinician and the patient. Despite having been hospitalized for 18 to 54 days and discharged for 14 to 51 days, physical function recovery was not satisfactory for patients in this cohort. The medium and long-term complications of SARS remain unknown resulting in uncertainty and anxiety. Some patients refrained from getting more physically active for fear of causing deterioration. Assessment of this cohort of patient to identify ongoing disease activity, pulmonary function impairment, evidence of myocarditis and psychological impact was warranted. The investigations were targeted at determining the extent of tachycardia and possible explanation(s). The major symptom was palpitation on slight exertion. Patients with resting heart rate at greater than 90 BPM were recruited because they are expected to have tachycardia response to greater than 100 BPM.

Patients with SARS had lymphopenia, anaemia, raised LDH and CRP at the acute stage.[6] The normal CBP, ESR, LFT, LDH, CK, CRP, as well as results of clinical assessment, suggest that ongoing active disease is unlikely. One patient had iron deficiency anaemia

**Table 4. Questionnaire**

| | QOL | | | | | |
|---|---|---|---|---|---|---|
| | Physical Health Domain | Psychological Health Domain | | Social Relationship Domain | Environment Domain | MFTE | Rehabilitation Programme |
| | | I | II | | | | |
| 1 | 75 | 63 | 69 | 50 | 75 | 20 | Y |
| 2 | *44 | *50 | *50 | 56 | 50 | 20 | Y |
| 3 | 69 | 69 | 75 | 100 | 75 | 19.4 | Y |
| 4 | 56 | *44 | *50 | 56 | 56 | 19.7 | Y |
| 5 | 75 | 75 | 75 | 81 | 81 | 18.8 | Y |
| 6 | 88 | 81 | 81 | 81 | 69 | 19.5 | Y |
| 7 | 63 | 75 | 75 | 75 | 88 | 18.7 | Y |
| 8 | 69 | 63 | 63 | 69 | 63 | 20 | N |
| 9 | 63 | 56 | 56 | 50 | 69 | 19.6 | Y |
| 10 | 63 | 56 | 63 | 75 | 63 | 20 | Y |
| 11 | 63 | *50 | *50 | 56 | 50 | 18.8 | N |
| 12 | 75 | 63 | 63 | 56 | 69 | 19.8 | N |
| 13 | 55 | *50 | 56 | 69 | 56 | 17.6 | Y |
| 14 | 69 | *50 | 56 | 56 | 69 | 20 | N |
| 15 | 63 | *25 | *38 | 56 | 56 | 19.2 | N |

QOL = Quality of Life Score; MFTE = Monitoring Functional Task Evaluation; *=Score ≤50

QOL score - Normal >75; MFTE score - Normal >20; Rehabilitation Programme Y = Yes, N = No

with a haemoglobin level of 10.6 g/dl that was similar at presentation. Normal thyroid function excluded thyrotoxicosis as the cause.

Coronarvirus infection had been demonstrated in animal model to cause an autoimmune myocarditis in rabbits that may progress to dilated cardiomyopathy.[14-16] Li et al reported reversible subclinical diastolic dysfunction without systolic impairment in the acute stage.[17] In our study, non-invasive cardiac investigations were done to document the extent of tachycardia and any significant cardiac complication. Holter monitoring demonstrated a minimal heart rate of 46 to 61 BPM and the sinus tachycardia at a rate of 114 to 163 BPM occurred in the daytime but not at night. Analysis of overall heart rate ≥100 BPM for each hour demonstrated occurrence between 9.00am to 9.00pm. in the awakening hours. This pattern of tachycardia is in keeping with physical deconditioning or anxiety state as the underlying cause, in response to physical activity or psychological stress. The normal SDNN in heart rate variability indicated a normal neurohumoral profile and excluded autonomic dysfunction.[18,19] No significant arrhythmia detected in the Holter monitoring in addition to the normal 12 lead ECG and SAECG signify a low risk of arrhythmia.[20] Normal troponin I, echocardiography and other negative cardiac investigations excluded myocarditis and cardiomyopathy.[21,22]

Residual pulmonary defect is another major concern. Residual CXR changes were mild and the pulmonary function impairment were not marked. These together with a normal blood gas would be unlikely to be a significant cause of sinus tachycardia with normal activity.

SARS is a new disease characterized by its highly contagious nature and severe pulmonary involvement with a 20% ICU admission rate. Our cohort of patients had a length of hospital stay ranging from 18 to 54 days, and they were advised to take infection precautions for another 14 days after discharge from hospital. The impact of this severe viral infection together with confinement would lead to physical deconditioning resulting in increased magnitude of tachycardia and decreased exercise tolerance. In addition, this cohort of patients had a more severe form of disease or various complications that caused prolonged hospitalization and hampered recovery. Four patients required ICU admission; 3 had secondary chest infection; one had urinary tract infection; one had idiopathic thrombocytopenia; one had pneumomediastinum and subcutaneous emphysema; one had steroid psychosis and 4 had anxiety depression. Patient 11 aged 62 is the eldest patient among this series combatable with a more protracted course of illness in the elderly. He had mild diastolic function that is quite common in patients with hypertension and gout. He did not have other identified complication at the acute stage.

All patients were treated with a protocol consisting of antimicrobials, ribavirin and hydrocortisone or methylprednisolone, in accordance with the guidelines issued by the Hong Kong Hospital Authority in April/May 2003.[23] Systemic steroid in the form of hydrocortisone or methyl prednisolone was prescribed for all patients, with high dose (pulsed) methyl-prednisolone given to 13 patients. All 15 patients had some degree of subjective proximal muscle weakness and this may contribute to impaired physical fitness. All patients did not have medications causing tachycardia at time of assessment.

All patients also received the antiviral agent ribavirin. High dose administration of this drug can cause bradycardia that was reversible on stopping the drug,[24,25] as observed in patient 6 in the cohort. However, there was no report of prolonged cardiotoxicity due to ribavirin. Additionally, ribavirin causes haemolytic anaemia in a high proportion of cases, and rapid onset of anaemia can cause tachycardia. Such haemolytic anaemia is usually quickly reversible and all patients in the cohort had haemoglobin at pre-illness levels by the time they were recruited into the study.

Subjective impairment of physical health, psychological well being and functional disability were evidenced by the high proportion of subjects with low QOL and MFTE scores. In fact, all patients had abnormal score in either one of these assessments. Severe impairment was predominant in the psychological well being domain. Anxiety state can be a cause of tachycardia in the daytime but not at night compatible with the pattern observed in the studied patients.

Furthermore, tachycardia, impairment of physical health, and impairment of psychological well being may all stem from severe physical deconditioning. The patients were offered a rehabilitation program conducted by the physiotherapy and occupational therapy departments of the hospital in out patient setting. Regular follow up at intervals of 1 to 3 months in the out-patient clinic as other post SARS patients to observe their progress was done. Observation for 12 to 20 months after discharge did not reveal significant cardiac symptom. Only 1 patient had complained of occasional palpitation with forceful heartbeat and requested further investigation. Repeated blood tests and Holter monitoring were normal.

## Limitations of the Study

The patients included in this study were a biased sample with more severe disease and complications. The original design of the study did not have a matched control of SARS patients with no tachycardia. The isolation and psychological stress of the SARS patients are unique. Patients suffering from other severe pneumonia of similar age group and no underlying co-morbidities were rare and could not be obtained as matched controls. Being a small cross-sectional study with no controls, many important questions cannot be adequately addressed. Such include risk factors for development of functional or psychological impairments and whether functional impairment was in fact contributed by steroid myopathy. Additionally, cardiopulmonary exercise testing would have provided data on exercise tolerance, oxygen consumption and anaerobic threshold, and would give a more comprehensive picture of the pathophysiology involved. The study was terminated because of the negative findings. Further cardiac investigations reassessment was not done because of the negative findings and further repeated investigations would poise undue stress and anxiety in the patients who were having immense medical and public attention. Only routine follow up as the other patients were done in the clinic.

## Conclusion

SARS is a severe systemic illness causing physical and psychological impairment in patients up to 2 months from onset of illness. In the absence of significant dysfunction of the cardiac, pulmonary, thyroid and haematological systems, sinus tachycardia on exertion is possibly attributable to physical deconditioning. In addition poor psychological state is likely to be a contributing factor. After appropriate rehabilitation programmes and follow up observations, no other suggested cause of tachycardia in the post SARS patients could be elucidated.

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**Appendix**

個人表現滿意度 Occupational Performance Appraisal Questionnaire
下列問題是關於你在最近兩星期對自己各方面表現的滿意程度
（請在答題簿上適當的格內填上所選之代表數字）

| | 極唔滿意 | 唔滿意 | 無話滿唔滿意 | 滿意 | 極滿意 |
|---|---|---|---|---|---|
| 1. 你對自己自我照顧的表現滿唔滿意？ | ❑1 | ❑2 | ❑3 | ❑4 | ❑5 |
| 2. 你對自己做家務的表現滿唔滿意？ | ❑ | ❑ | ❑ | ❑ | ❑ |
| 3. 你對自己工作的表現滿唔滿意？（工作指賺錢的工作或生意、義工、讀書、照顧家庭包括料理家務、在家照顧小孩或老人等） | ❑ | ❑ | ❑ | ❑ | ❑ |
| 4. 你對自己與人相處或溝通的表現滿唔滿意？ | ❑ | ❑ | ❑ | ❑ | ❑ |
| 5. 你對自己參與康樂或消遣活動的表現滿唔滿意？ | ❑ | ❑ | ❑ | ❑ | ❑ |
| 6. 你對自己應用公共設施的表現滿唔滿意？（應用公共設施包括搭車、買餸、去郵局、銀行等。） | ❑ | ❑ | ❑ | ❑ | ❑ |
| 7. 你對自己均衡分配日常活動時間的表現滿唔滿意？（日常活動是指工作、休息、娛樂社交等活動。） | ❑ | ❑ | ❑ | ❑ | ❑ |
| | 唔快樂 | 小小快樂 | 某程度快樂 | 好大程度快樂 | 極快樂 |
| 8. 整體來講，你覺得你的生活快唔快樂？ | ❑1 | ❑2 | ❑3 | ❑4 | ❑5 |

**Appendix** (con't)

| **Occupational Therapy**<br>**SARS Patient Evaluation**<br>**Princess Margaret Hospital** | Please Use Block Letter or Affix Label<br>**Name : _____ (  )**<br>**Sex / age : _____ Ward / Bed :** |
|---|---|

Monitored Functional Task Evaluation/ADL Checklist Date :

Resting $SaO_2$ / Pulse : ____ % /____

Oxygen Desaturation : heavy / moderate / mild

Dyspnea (Max) : ____ / 10 Exertion (Max) : ____/10 Tiredness (Max) : ___/10 Total marks: ____ /20

| **Task** | **1**<br>**Indoor Mobility** | **2**<br>**Lifting 3 kg** | **3**<br>**Stepping** | **4**<br>**Carrying 6 kg** | **5**<br>**Sit<=>Stand** |
|---|---|---|---|---|---|
| 2 mins completed<br>Duration | yes / no<br>: | yes / no<br>: | yes / no<br>: | Yes / no<br>: | yes / no<br>: |
| Number / 2 mins | | | | | |
| Pace | even / rush | even / rush | even / rush | even / rush | even / rush |
| RPD / RPE / RPT | / / | / / | / / | / / | / / |
| Recovery | 2 mins / | 2 mins / | 2 mins / | 2 mins / | 2 mins / |
| $SaO_2$ | % | % | % | % | % |
| Pulse Rate | | | | | |
| Marks | | | | | |

Lift role : ____ Premorbid ADL level : ____ (marks ); Present ADL level : ____ (marks )

| **ADL level** | **Activity** | **Premorbid** | **Present** | **Marks** |
|---|---|---|---|---|
| Level 1 | resting on chair / watching TV | | | 1 |
| | feeding | | | |
| | grooming (e.g. wringing towel / shaving) | | | 2 |
| | managing bowel | | | |
| Level 2 | transfers to / from bed | | | 3 |
| | dressing garments | | | |
| | dressing shoes / socks | | | 4 |
| | indoor mobility | | | |
| Level 3 | bathing (shower / basin / bathtub) | | | 5 |
| | washing hair | | | |
| | simple households (e.g. washing utensils) | | | 6 |
| | simple cooking (e.g. rice-cooker) | | | |
| Level 4 | walking up one flight of stairs | | | 7 |
| | strolling for 20 mins | | | |
| | complex households (e.g. bedmaking) | | | 8 |
| | complex cooking (e.g. frying) | | | |
| Level 5 | laundry / ironing | | | 9 |
| | shopping (carrying 61bs for 15 mins) | | | |
| | public transport (taxi / bus) by self | | | 10 |
| | heavy households (e.g. mopping floor) | | | |

# A Systematic Review on the Role of Diet and Nutritional Supplements for Prevention of Cardiovascular Diseases

YAP-HANG CHAN, HUNG-FAT TSE, SHEUNG-WAI LI, CHU-PAK LAU

From Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR

**CHAN ET AL.:** ***A Systematic Review on the Role of Diet and Nutritional Supplements for Prevention of Cardiovascular Diseases.*** *According to the diet-heart hypothesis, dietary factors play a pivotal role in atherogenesis. Modulation of the diet has therefore been considered a means to achieve better cardiovascular health and a major subject of public health importance. Five major types of diet have been identified: the low-carbohydrate diet, low glycemic index diet, very-low-fat diet, the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet. Clinical studies have shown that none of these diets are universally efficacious. The results from various clinical trials on the use of diet to prevent cardiovascular diseases are commonly conflicting due to unadjusted caloric intake and concurrent changes in alternative food consumption. Nonetheless, a diet rich in fresh fruits and vegetables with polyunsaturated fat intake from plant oil and fish, but restricted intake of high glycemic index carbohydrates is generally advisable. The importance of an individualized approach and holistic lifestyle commitments including regular exercise should be emphasized. Currently, there is limited data on nutritional supplements in heart health. Recent clinical trials have shown that vitamins C and E supplement are ineffective, and the use of high dose vitamin B and folate is actually harmful. Physicians should therefore be cautious in advising on and prescribing these supplements. Phytoestrogen represents a recently focused branch of nutritional supplement with potentially cardioprotective implications. Its recommendations should depend upon further randomized controlled trials. (J HK Coll Cardiol 2005;13:68-84)*

*Coronary artery disease, diet, phytoestrogen, prevention, vitamins*

**摘要**

基於飲食和心臟病關係的假設，飲食在動脈粥樣硬化中扮演着重要的角色。因此改變飲食結構被認爲是改善心腦血管健康的一種方法，並且成爲公共健康的一項重要課題。我們已經確定了五種主要類型的飲食：低碳水化合物飲食，低糖指數飲食，低脂肪飲食，地中海式飲食和阻斷高血壓方式的飲食。臨床研究表明沒有任何一種飲食類型是普遍有效的。運用飲食來防止心血管疾病的各種臨床試驗，其結果往往相互衝突，原因在於飲食的熱量攝入未加調整，和選擇性食物攝入的改變。儘管如此，飲食中含豐富新鮮水果和蔬菜，以植物油和魚類提供多聚不飽和脂肪酸，並且限制高糖指數的碳水化合物攝入，往往這樣的飲食結構是值得推薦的。我們應當強調包括經常性鍛煉在內的、個體化方法和整體機能生活方式的重要意義。最近的臨床研究顯示補充維生素C 和E 是沒有效用的，而大劑量的維生素 B 和葉酸實際上是有害的。因此，醫生們在推薦和處方這些補充物質時需要格外謹慎。植物類雌激素對於心血管具有潛在的保護作用，這代表着新近營養補充物的關注焦點。是否值得推薦還需進一步的隨機對照研究。

關鍵詞：冠心動脈性心臟病　飲食　植物類雌激素　預防　維生素

Address for reprints: Prof. Chu-Pak Lau, MD, Cardiology Division Chief (Academic)
Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Tel: (852) 2855 4244; Fax: (852) 2855 6304

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## Introduction

Although the role of diet in atherogenesis has been questioned for nearly a century, a large part of this question remains unanswered today. The role of diet in both prevention and management of coronary artery disease (CAD) remained inconclusive and highly controversial. Current nutritional thoughts have been dominated with the traditional diet-heart hypothesis,[1-3] which is characterized by the causal relationships between serum cholesterol elevation and atherosclerotic heart diseases as a consequence to dietary intake of saturated fat (Figure 1). This philosophy has led to the most unparalleled dietary recommendation ever: that a low-fat diet is heart-healthy and preventive against cardiovascular diseases. For instance, the latest guideline of American Heart Association in 2000 recommends a low-fat diet in which 55% of total calories is derived from carbohydrates, 30% from fat, the remaining 15% from proteins, with cholesterol not exceeding 300 mg per day.[4] However, this dietary recommendation has resulted in a paradoxical uprising trend of Type II diabetes, obesity and metabolic syndrome in the developed world.[1] The prevalence of obesity in the United States had surged new heights and increased by more than 60% in ten years since 1991.[5] This epidemic of obesity and related syndromes could simply be a result of unrestricted carbohydrate intake, which was indirectly promoted by a low-fat diet.

## Diet and Cardiovascular Diseases

With this increasing frustration and the realistic eagerness of the population to find alternative ways of effective slimming, the diet-heart hypothesis could no longer stay unshaken. Both scientists and dieticians thus have started to explore other dietary approaches in heart health, the best noted categories include: 1) low-carbohydrate diet; 2) low Glycemic Index (GI) diet; 3) very-low-fat diet; 4) the Mediterranean diet; and 5) the Dietary Approaches to Stop Hypertension (DASH) diet. Table 1 summarizes the current status of different diets used for heart health, and other factors such as personal lifestyle and preference that will also affect their efficacy and sustainability at different time and places. It is thus unrealistic to expect there could ever be a single diet, which could serve the purpose of everyone. Generalized dietary approaches to cardiovascular heath, however, could be extracted with the available evidence and are summarized in Table 2. Indeed, the US Department of Agriculture has recently

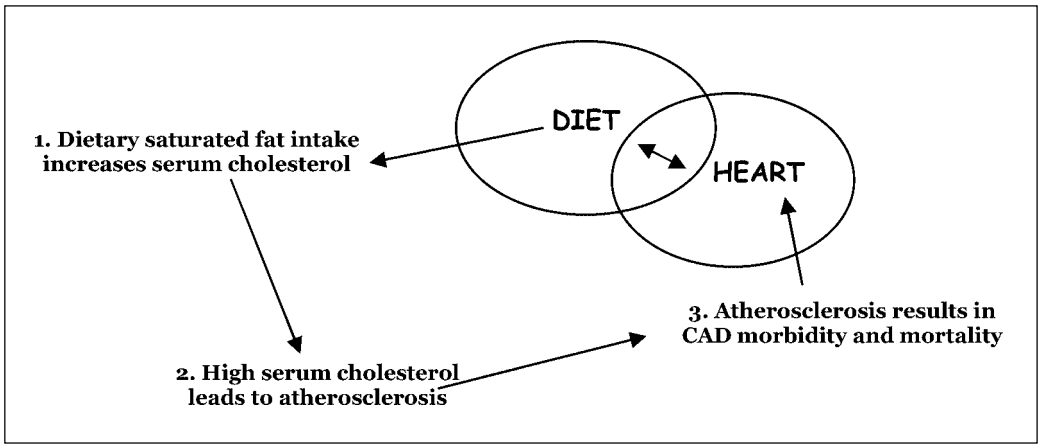


**Figure 1.** *The diet-heart hypothesis. The conventional diet-heart hypothesis is essenced by a syllogism of dietary saturated fat intake, serum cholesterol and atherosclerosis. It has however remained controversial and is now increasingly questioned due to the emerging role of polyunsaturated fatty acids as a component of dietary fat which may potentially confer cardiovascular benefits.*

**Table 1. Summary on the characteristics of the major types of diets**

| Type of diet | Composition | Current knowledge | Sustainability |
|---|---|---|---|
| Atkins' Diet | 68% fat, 27% protein,<br>5% carbohydrates;<br>extreme carbohydrate restriction in the first 2 weeks | Short-term weight loss;<br>Sustained improvements in lipid profile at 1 year;<br>Unknown long-term effects | Low to moderate |
| Low GI diet | Complex carbohydrates in preference to simple sugars | Low GI confers to greater weight loss;<br>Unknown effects in cardiovascular diseases;<br>Possible negative association with diabetes | Moderate to high |
| Very-low-fat diet | <15% fat,<br>15 % protein,<br>70% carbohydrates | Possible reduction in cardiac event risk;<br>Intensive life-style changes often corporated;<br>Self-motivation & sustainability strongly required | Low |
| Mediterranean diet | High consumption of fruits, vegetables, legumes & grains;<br>foods with high monosaturated/ saturated fats ratio;<br>moderate dairy products & wine consumption; reduce meat consumption; high intake of Omega-3 fatty acids | Secondary prevention of acute & fatal myocardial infarction;<br>Reduction of sudden cardiac deathby its anti-arrhythmic effects;<br>Unknown effects of mercury exposure | High |
| DASH | Similar to Mediterranean diet;<br>high in potassium, calcium, magnesium and fiber | Reduced both systolic and diastolic blood pressure; greatest effect among African, Americans and hypertensive individuals | Moderate to high |

**Table 2. Summary of healthy dietary approaches**

Generalized approaches to a healthier diet:

↓ Carbohydrate intake (Refined and high GI carbohydrates)

↑ Consumption of fruits, vegetables & whole grains

↑ Polyunsaturated fat intake from plants oils & fish

→ Moderate intake of low-fat dairy products & nuts

announced a new food pyramid - My Pyramid which emphasizes the need of individualized approaches and the element of exercise in promoting heart health through lifestyle changes (Figure 2).

## Low-carbohydrate Diets

There are numerous forms of low-carbohydrate diets such as the Zone Diet, Protein Power, Sugar Busters and the Stillman Diet, but the Atkins' Diet remains the most popular variant in recent years. The Atkin's Diet recommends vigorous carbohydrate restriction, regardless of simple or complex sugars, to 28 g per day in the first 2 weeks. This is then followed by gradual increment up to 35 g per day to achieve ongoing weight loss. In this diet, 68 % of calories comes from fat, 27% from proteins and the remaining 5% from carbohydrates.[2,6]

In the Atkins' Diet philosophy, extreme carbohydrate restriction renders the body to derive energy through oxidative catabolism of fatty acids. Whilst this may serve the purpose of fat-burning, it produces significant amount of ketones being excreted by the urine, thus contributing to rapid initial weight loss through diuresis. This encouraging initial response may, therefore, be disguising. The high protein and fat content of the diet is highly satiating, and the limited food choices also reduces spontaneous food intake. Besides that reduced carbohydrate intake plays a role in curtailing caloric gain, ketosis was also found to suppress appetite. These together may explain the short-term weight reduction with Atkins' Diet.[2,6]

Bravata et al[7] performed a systematic review from 1966 to 2003 to evaluate the effects of low-carbohydrate diets on body weight and serum cardiovascular risk markers. He concluded that weight loss achieved through this dietary approach was principally associated with decreased caloric intake and increased duration between meals, but not with reduction of carbohydrate

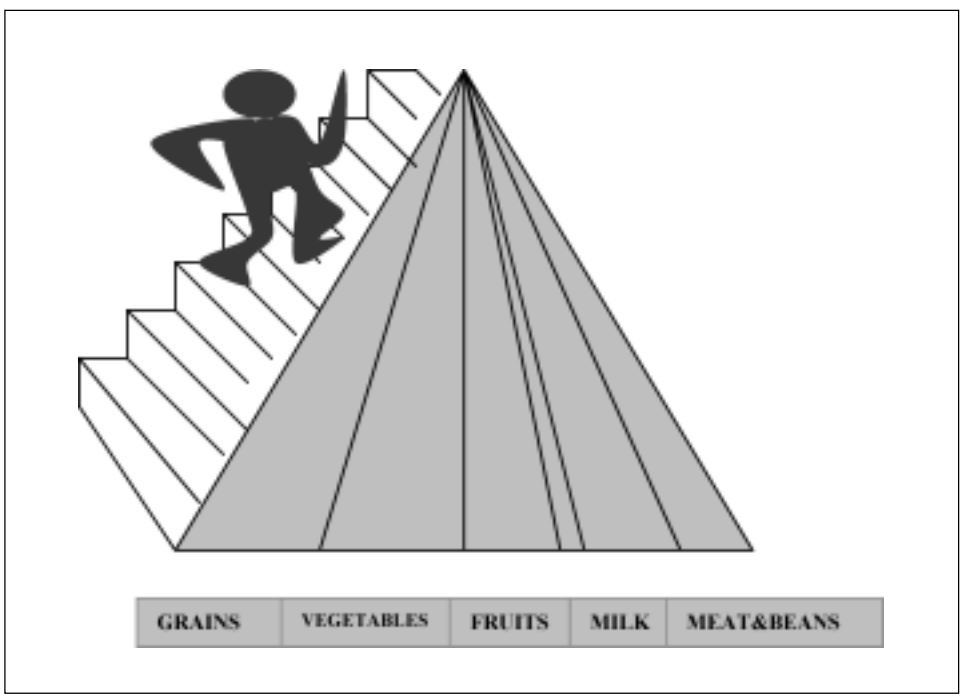


**Figure 2.** *My Pyramid: Steps to a Healthier You. The latest food pyramid suggested by the US Department of Agriculture (USDA). The 6 panels represent a wide variety of food groups (grains, vegetables, fruits, milk, oils, meat and beans) in a healthy diet. The running cartoon figure on the left conveys a message of the importance of exercise. One size doesn't fit all – this modified pyramid emphasizes a more individualized approach to improve health by making modest changes in diet and incorporating regular physical activity into daily living.*

content per se. However, the studies included in the review had been highly heterogeneous in design, carbohydrate and calorie content, as well as duration between meals.

A total of four large randomized controlled trials have compared the efficacy of a low-carbohydrate diet with traditional low-fat diet. Stern et al[8] randomized 132 obese subjects to receive either a low-carbohydrate or a low-fat diet for 12 months. Their mean body-mass index was 43 and they had a high prevalence of diabetes (39%) and metabolic syndrome (43%). At 6-month, the low-carbohydrate diet group showed greater weight loss, higher high-density lipoprotein (HDL) cholesterol level, lower triglyceride levels and improved insulin sensitivity, independent of the use of hypoglycemic and lipid-lowering medication, than the low-fat diet group. However, the weight change difference between the two groups became insignificant at 12-month.

Foster et al[9] randomized 63 obese men and women to receive low-carbohydrate, high-protein, high-fat diet or a low-calorie, high carbohydrate, low-fat (conventional) diet for 12 months. Similarly, subjects in the low-carbohydrate diet lost more weight (~4%) than the low-fat group up to 6-month, and but the difference again became insignificant by 12-month. Throughout the course of the study, the low-carbohydrate group had lower triglycerides and higher HDL cholesterol than the low-calorie group. In this study, the adherence and attrition rate were high in both groups.

Brehm et al[10] assigned 53 healthy, obese female subjects to either a low-carbohydrate diet or a calorie-restricted diet (30% fat) for 6 months. By 3 and 6 months, weight and body fat reduction were significantly greater in the low-carbohydrate group, although there was no difference observed in the two diet groups in terms of serum lipids, fasting glucose, insulin level and blood pressure.

Yancy et al[11] randomized 120 overweight, hyperlipidaemic patients to receive either a low-carbohydrate diet or low-fat diet group. Both groups received exercise recommendation, and the low-carbohydrate group also received additional nutritional supplementation. At 6-month, the low-carbohydrate group had greater weight reduction as well as larger decrease in triglycerides and increase in HDL cholesterol. The observed effect, however, was confounded by the nutritional supplementation.

Although these four randomized studies consistently demonstrated that low-carbohydrate diets could achieve a greater weight loss at 6 months, the calories intake was not controlled. Therefore, the changes in appetite associated with low-carbohydrate diet might affect the calorie intake and accounted for the difference in the weight reduction. Segal-Isaacson et al[12] investigated how weight loss and metabolism are affected by low-carbohydrate and low-fat diet when energy and protein contents are held constant, and dietary fat and carbohydrates are relatively adjusted. In this study, 4 postmenopausal overweight female were randomized in cross-over fashion to receive either a low-carbohydrate or a low-fat diet for 6 weeks. They showed no significant differences in weight loss, serum lipid, insulin, and glucose between the two groups. However, these findings need to be confirmed by future studies in a large cohort of subjects.

In summary, low-carbohydrate diet was effective for weight reduction in short-term, but this result was not sustained at long-term follow-up. The initial encouraging result of this diet often provides motivation for adherence in some patients. Furthermore, the potential adverse effects of low-carbohydrate diet have not been fully evaluated. In fact, the AHA Scientific Advisory has warned that this type of diet might cause metabolically induced kidney and liver damage, as well as worsening of CAD.[1]

## Low Glycemic Index Diets

The GI is a measure of the blood glucose response to the intake of a specified type of carbohydrate. By obtaining the glycemic load, a product of dietary GI and the total dietary carbohydrate, the glycemic effect of a diet can be estimated.[2] It has been proposed that the elevated free fatty acid levels and increased hunger caused by a high GI diet predisposes individuals to the risk of obesity, diabetes and cardiovascular diseases. The increased oxidative stress can lead to endothelial damage and pro-coagulatory activity. Starch and sugars, for instance, typical of high GI, tend to cause hyper-insulinemia and may promote the development of Type

II diabetes.[1]

The South Beach Diet is a common variant of a low-GI diet, characterized by an initial two-week of vigorous carbohydrate restriction, and then a maintenance phase which encourages intake of fruits, vegetables, whole grains, polyunsaturated fats, nuts and dairy products. Despite the similar initial carbohydrate restriction with the Atkins' Diet, it encourages the intake of lean protein such as fish and poultry, and allows olive oil as a source of mono- and polyunsaturated fat. Clinical studies have found that a low-GI diet confers to greater weight loss than a high-GI diet, and may in addition play a role in modulating HDL metabolism in inverse proportions.[13] Frost et al have suggested that every 15-unit increase in GI is associated with a 0.06 mmol/L decrease in HDL cholesterol.[14] However the confounders in these studies need to be taken into consideration; as food preparation and variation may change the GI, while recall bias may be present in self-reporting.

## Very-low-fat Diets

By definition this allows less than 15% of total calories from fat, 15% from protein and 70% from carbohydrates, assuming an equal distribution of saturated, monounsaturated and polyunsaturated fats. There is some but inconclusive clinical evidence that a very-low-fat diet together with intense life-style changes including exercises may provide protection against cardiovascular diseases, yet high self-motivation is needed and attrition rate of the diet is a major concern.

## The Mediterranean Diet

The dietary pattern of inhabitants around the Mediterranean has been indicated to confer heart protection. The key components of Mediterranean diet are: 1) high consumption of fruits, vegetables, legumes and grains; 2) foods with high mono-saturated to saturated fats ratio; 3) moderate consumption of dairy products and wine; 4) low consumption of meat and meat products and 5) consumption of olive oil as the principal source of fat.[2]

It is worth noting that no single aspect of the diet has contributed to its extent of weight-losing effect and the reduction of cardiovascular morbidities and mortalities. Nevertheless, omega-3 polyunsaturated fatty acids have always been a major focus of the observed cardioprotective benefits. The omega-3 fatty acids encompasses a spectrum of compounds including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fatty fish, as well as alpha-linolenic acid (ALA) found in nuts, flaxseed and soybean oil. They are suggested to possess anti-arrhythmic effect which confers to their ability to reduce sudden cardiac death.[15] They may also decrease the arachidonic acid content of cell membranes, down-regulate the gene expression of adhesion molecules and inhibit proinflammatory cytokine synthesis including tumour necrosis factor-Alpha, interleukin-1 and interleukin-2. They are also found to lower triglyceride level, inhibit endothelial cell activation, decrease thrombotic tendency and improve endothelial dysfunction in diabetics.[12]

A systemic review of 11 cohort studies performed by Marckmann et al in 1999[16] concluded an inverse association between fish intake and coronary mortality, which was stronger for fatal than non-fatal myocardial infarction. It is also observed that the benefits so derived were more significant in populations at higher risks. Results from further prospective studies found that consumption of 2 or more servings of fish per week was associated with 30% lower risk of CAD in women.

There are some evidences that the use of omega-3 fatty acids in the secondary prevention of cardiovascular diseases confers a benefit in the reduction of all-cause mortality and fatal myocardial infarction. The largest randomized, controlled trial, the GISSI-Prevenzione Trial followed 11234 patients and found that fish oil supplement of 1 g of EPA/DHA per day reduces 20% of cardiac death, nonfatal myocardial infarction and nonfatal stroke, with the greatest benefit observed in sudden cardiac death (reduction by 45%).[17] Previous studies supported the view that the benefits induced by long-chain n-3 PUFA in seafood are specific to fatal CAD, due primarily to a reduction in fatal arrhythmias, rather than total coronary events. There is also possibly a threshold effect.[3,17] The available evidence, therefore, advocates the clinical and public health recommendation for dietary intake of at least 1 fatty fish meal per week, although there are concerns

such as the underestimated undesirable effect of contaminant intake due to pollution.[3]

Mediterranean diet has been shown to be effective in secondary prevention of acute and fatal myocardial infarction.[18-23] The ability of Mediterranean diet to induce weight loss, lower C-reactive protein level, improve lipid profiles, and reduce insulin resistance and prevalence of metabolic syndrome warrants further research and application. The current evidence indicated 3 strategies in this diet preventing CAD:[2] 1) substituting non-hydrogenated unsaturated fats for saturated and trans-fats; 2) increasing consumption of omega-3 fatty acids; and 3) consuming more fruits, vegetables, nuts, and whole grains.

### Dietary Approaches to Stop Hypertension (DASH) Diet

The DASH diet is similar to the Mediterranean diet, which emphasizes a high intake of fruits, vegetables, low-fat fairy products, whole grains, nuts, fish, poultry, and reduce intake of total and saturated fats. This diet is mainly aimed for blood pressure reduction.[2] DASH diet is high in potassium, calcium, magnesium and fiber, but not for sodium. Sacks et al[24] conducted the DASH-Sodium Trial to evaluate the effect of different levels of dietary sodium intake in conjunction with the DASH diet for blood pressure reduction. A total of 412 subjects with or without hypertension were randomly assigned with either a control diet or the DASH diet. In each arm, there were 3 different levels of sodium intake: high, intermediate, and low, in which participants follow each for 30 consecutive days in random order. The results of this study confirmed that the DASH diet alone is able to reduce systolic and diastolic blood pressure by 5.5 mmHg and 3.3 mmHg respectively. However, in the control group, sodium restriction had a dose-response relationship with reduction in blood pressure. While this relationship persisted for the DASH diet, the magnitude was comparatively smaller and was only significant between the high and low, but not for intermediate sodium group. Therefore, the DASH diet and sodium restriction exhibits a synergistic effect in substantiating reduction in blood pressure. In the clinical trial setting, this diet has been applied in a very controlled setting and its implementation in the general public should be supported by further studies in general population. Long-term health benefits by sodium restriction will also depend upon the ability of people to make long-standing dietary changes and the more widely available low-sodium food.

## Nutritional Supplements in Cardiovascular Health

Table 3 summarizes the current clinical evidences on the use anti-oxidatant vitamin for prevention of cardiovascular diseases. Despite all the initial encouraging results from epidemiological observation studies,[25-27] randomized controlled trial failed to demonstrate any beneficial effects of these vitamins in preventing cardiovascular diseases.[33,34,40-42]

### Vitamin C

There have been extensive investigations, especially experimental and epidemiological studies, on the possible beneficial effects of vitamin C to prevent cardiovascular diseases. Evidences also suggest that vitamin C has a potential of lowering blood pressure and cholesterol, as well as improving endothelial function.

In the WHO MONICA study,[25] an inverse relationship was observed between vitamin C plasma level and mortality from CAD. Similarly, in the larger scale prospective Nurses' Health Study in 1980,[25] 85118 female nurses had their vitamin C intake assessed with a questionnaire and followed up for 16 years. The use of vitamin C supplement was associated with a 27% relative risk reduction for the development of CAD. However, among those who did not take Vitamin C supplements, there was no association between dietary intake and CAD incidence. In another 5-year prospective study of 1605 middle-aged Finnish men,[26] vitamin C-deficient individuals (defined as plasma level <11.4 umol/L) were found to have a 2.5 times relative risk of myocardial infarction. For men with plasma level of vitamin C greater than 11.4 umol/L, no differences in fatal or non-fatal myocardial infarction outcomes were observed. In the NHANES I study,[27] 11,348 non-institutionalized U.S. adults aged 25-74 years were

**Table 3. Recent major randomized controlled trials on vitamin C & E supplements in relation to cardiovascular health**

| Trial | Population | Intervention | Follow-up | Outcomes |
|---|---|---|---|---|
| MRC/BHF Heart Protection Study[33] | 20536 men & women aged 40-80; with coronary or other occlusive arterial diseases or diabetes | 600 mg vitamin E + 250 mg vitamin C + 20 mg beta-carotene daily | 5 years | No significant difference in all-cause or cardiovascular mortalities, fatal or non-fatal MI, fatal or non-fatal stroke |
| St. Francis Heart Study[34] | 1005 men & women with coronary calcium score at or above 80th percentile | Vitamin C 1 g + Vitamin E 1000U + Atorvastatin 20 mg daily or matching placebo | Mean 4.3 years | ↓ Serum cholesterol 26.5-30.4%<br>↓ LDL cholesterol 39.1-43.4%<br>↓ Triglycerides 11.2-17.0%<br>No reduction in atherosclerotic cardiovascular disease events |
| ASAP Trial[35] | 520 men & women with serum cholesterol >5.0 mmol/L | Vitamin E 136 IU + 250 mg slow-release vitamin C twice daily | 6 years | Atherosclerotic progression as measure by common carotid artery – intima-media thickness slowed down in male with intervention |
| HOPE Study[40] | 2545 women & 6996 men with cardiovascular diseases or diabetes | 400 IU Vitamin E or matching placebo + 10 mg ramiprilor matching placebo | Mean 4.5 years | No significant difference in cardiovascular deaths or other outcomes |
| MICRO-HOPE[41] | 3654 diabetes patients | 400 IU Vitamin E or matching placebo + 10 mg ramiprilor matching placebo | Mean 4.5 years | No significant difference in cardiovascular or microvascular outcomes |
| HOPE-TOO Trial[42] | 3994 men & women with cardiovascular diseases or diabetes | Vitamin E 400 IU or matching placebo | Mean 7.0 years | No significant difference in major cardiovascular events; treatment increases risk for heart failure |

studied and an inverse cardiovascular mortality was observed with a vitamin C supplemental intake of more than 50 mg daily. It was also found that leukocyte ascorbic acid level was significantly lower in patients with coronary atherosclerosis. The leukocyte ascorbic acid level is a stable indicator of vitamin C store in the body. Vita et al demonstrated that the leukocyte ascorbic level but not the extent of atherosclerosis, was found to be a predictor of unstable coronary syndrome.[28] These findings suggest that the beneficial effects by vitamin C may result in part by influencing lesion activity rather than retarding the overall disease progression.

Such beneficial effects of vitamin C is believed to arise from its anti-oxidant properties which enhances the effect of endothelium-derived nitric oxide by blocking oxidants such as superoxide and oxidized low-density lipoprotein (LDL), and thus sparing intracellular glutathione and regenerating vitamin E. This mechanism was supported in a study by Kugiyama et al[29] who found that intracoronary vitamin C infusion restored angiographically proven coronary spasm induced by acetylcholine infusion and reduced thiobarbituric substances. Nevertheless, pathways beyond inhibiting LDL oxidation also deserves further exploration, which essentially include effects of reduced formation of reactive oxygen species, improved vascular tissue integrity, reduced leukocyte adhesion and platelet aggregation, and enhancement of vascular relaxation

ability.[30]

Despite theoretical plausibility, results from related clinical trials remained conflicting. A recent randomized controlled trial on 30 subjects undergoing cardiac catheterization for evaluation of CAD by Kinlay et al[31] had found no significant improvement on endothelial vasomotor function after 6 months oral administration of vitamins C and E. There is, however, evidence that vitamin C was able to selectively improve large artery compliance in postmenopausal women.[32]

The effects of vitamin C supplementation on heart disease prevention as observed from more recent, larger-scaled clinical trials have not been encouraging. In the MRC/BHF Heart Protection Study, 20536 high risk individuals with either CAD or other occlusive arterial diseases, or diabetes, were randomly allocated to receive combined 600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily or matching placebo. After a mean treatment period of 5 years, despite a substantial increase in serum vitamin concentrations, there were no significant differences in all-cause mortality, deaths due to vascular or non-vascular causes, and fatal or non-fatal myocardial infarction compared to placebo.[33]

In the St. Francis Heart Study Randomized Clinical Trial,[34] 1005 subjects with coronary calcium scores at or above the 80th percentile for age and gender were treated with alpha-tocopherol, vitamin C and low doses of atorvastatin. After a mean treatment period of 4.3 years, no change was observed in the progression of coronary calcification and there was no significant reduction in atherosclerotic cardiovascular disease events.

One of the major limitations of these studies is the difficulty to isolate the effect of vitamin C from co-administered supplements, such as vitamin E. The apparently inconsistent findings from clinical trials and epidemiological studies may also be explained by some possible confounding factors. The recent British women's Heart and Health Study[36] suggests that vitamin C intake was not associated with CAD risk once life course socioeconomic position was taken into consideration. It has been argued that vitamin C intake is truly associated with socioeconomic position and previous positive epidemiological findings may have just been a failure of recognizing confounders. Publication bias is another important factor to consider. Thus further studies must be conducted before such supplementation can be advised.

Nevertheless, on the ground of conflicting evidence, it is appropriate to stay conservative in using vitamin C as a supplement to protect against cardiovascular diseases. In general, increasing intake of fresh citrus fruits is advisable because they also contain fibres and other essential nutrients.

## Vitamin E

Among the various forms of vitamin E, alpha-tocopherol represents the most biologically important form, which is predominantly found inside the LDL particles. As a result of its antioxidant properties, vitamin E is believed to reduce Apo B and LDL susceptibility to peroxidation by free radicals. In patients with CAD, it was demonstrated that LDL susceptibility to oxidation was reduced by a combination of vitamins E, C and beta-carotene. It was also reported from a randomized controlled trial that vitamin E supplementation alone was able to reduce lipid peroxidation in vivo.[37] Multiple epidemiological studies suggested that vitamin E intake was associated with a lower risk of CAD. For instance, the Nurses Health Study (1980) has found a 41% risk reduction for CAD in nonsmokers with a supplement of 100 IU Vitamin E daily for more than 2 years.[38] The Cambridge Heart Antioxidant Study Trial also demonstrated a 77% reduction of nonfatal myocardial infarction by treatment with alpha-tocopherol.[39]

The role of vitamin E for patients with high risk of CAD has recently been addressed. In the Heart Outcomes Prevention Evaluation (HOPE) Study,[40] 2545 women and 6996 men aged 55 or above with cardiovascular diseases or diabetes were randomly assigned to receive either a 400 IU of vitamin E daily or matching placebo and either ramipril or matching placebo. After a mean of 4.5 years, there were no significant differences in the number of cardiovascular deaths and the incidence of secondary cardiovascular outcomes including unstable angina, congestive heart failure, revascularization, limb amputation and diabetic complications. In a sub-study of HOPE-the Microalbuminuria Cardiovascular Renal Outcomes

(MICRO-HOPE) study,[41] which evaluated the impact of vitamin E on cardiovascular and microvascular outcomes in 3654 diabetes patients, there was also no beneficial effect on cardiovascular or renal outcomes by vitamin E supplement could be found. The HOPE study has been further extended for 4 years from 1999 to 2003 to observe the long-term effects of vitamin E supplementation. Again, it was found that vitamin E did not prevent major cardiovascular events or cancer, and might even increase the risk for heart failure.[42] Thus, there is currently no indication to use vitamin E supplements for prevention of cardiovascular diseases.

## Vitamin B and Folate

The proposed mechanisms through which vitamin B might lower cardiovascular risks stems from the link between atherosclerosis and homocysteine, the later being an amino acid normally found in blood from catabolism of dietary proteins. Elevated serum homocysteine in conditions such as cystathionine beta synthetase deficiency, are associated with accelerated atherosclerosis and increased mortality risk from cardiovascular diseases. However, there is no definitive link proven between reduction of homocysteine levels and prevention of CAD, or any evidence that vitamin B and folate supplementation could reduce the incidence of CAD.

Recently, the Norwegian Vitamin Trial (NORVIT)[43] was presented at the European Society of Cardiology Congress 2005 and reported that vitamin B and folic acid offer no secondary protection against cardiovascular diseases. In NORVIT, 3,749 patients who had acute myocardial infarction within the previous 7 days were assigned to take B vitamins or placebo for more than 3 years in addition to the standard management. There were 4 treatment groups: 0.8 mg folic acid per day, 40 mg vitamin B-6 per day, both folic acid and 40 mg vitamin B-6 per day, or placebo. After 3.5 years, there were no significant differences in non-fatal/fatal myocardial infarction and non-fatal/fatal stroke between groups taking vitamin B-6, folic acid and placebo, despite the fact that homocysteine levels were lowered by up to 30 per cent. However, the risk of myocardial infarction and stroke was increased by 20% in the group where folic acid and vitamin B-6 were co-administered. This implies that high doses of vitamin B are ineffective for secondary cardiac prevention, and that the combination of folic acid and B6 may actually increase cardiovascular risk. Therefore, routine supplementation with the B vitamins should not be advocated for cardiovascular disease prevention.

## N-3 Polyunsaturated Fatty Acids

This was discussed in the foregoing in conjunction with the Mediterranean diet. The major mechanism of the benefit of polyunsaturated fatty acids is its effect on increasing omega-3 fatty acid in the cell membrane. This leads to altered cardiac ion channel function and reduces ventricular vulnerability to ventricular fibrillation.[3] It is noted that in the Diet and Reinfarction Trial (DART),[21] patients consuming fatty fish had better survival despite indistinguishable reinfarction rates from the control group. The lower mortality could therefore be possibly explained by a decrease in sudden cardiac death elicited by ventricular tachyarrhythmias.[44] Mozaffarian et al[45] analyzed 30 randomized, double-blind, placebo-controlled trials on the effect of fish oil on heart rate in a meta-analysis. It was found in the overall pooled estimate that fish oil decreased heart rate by 1.6 beats per minutes as compared to placebo. In particular, such effect was only evident in trials where the baseline median heart rate was greater than or equal to 69 beats per minutes, represented by a respective reduction of 2.5 beats per minutes. Similarly, a significant heart rate reduction was observed exclusively in trials with a minimum duration of 12 weeks. Thus fish oil reduced heart rate particularly with higher baseline heart rate or longer duration of intervention. It should be further noted that any heart rate reduction on fish oil intake was not related to the fish oil dosage. The findings from the study reinforce the hypothesis that cardiac electrophysiology is either directly or indirectly influenced by fish oil consumption. Given that a higher heart rate is reported to be a major risk factor for sudden cardiac death,[46-50] the heart rate reduction concerned here may in part account for the observed inverse relationship between fish oil intake and fatal arrhythmias.[15,51] The stronger reduction in trials of longer duration may simply reflect the time needed for the omega-3 fatty acids to be incorporated into the

cellular structures. Alternatively, it is also possible that omega-3 fatty acids favorably influence heart rate variability and autonomic tone. Other than these stated potential mechanisms, omega-3 fatty acid is also proposed to result in a reduced systemic vascular resistance, which lowers blood pressure[45,52] and left ventricular afterload, hence improving diastolic function. The reduced heart rate can therefore be an indirect result of enhanced ventricular efficiency. Nonetheless, the approximately 5% lower risk of sudden death corresponding to the 1.6 beats per minutes heart rate reduction[50] cannot explain fully the results from the majority of previous studies, and thus further investigation of other cardioprotective roles played by omega-3 fatty acids is warranted.

Clinical trials of omega-3 fatty acids so far mainly focused on its use in patients with established CAD. Its exploration in retarding restenosis[53,54] after percutaneous coronary intervention has become less meaningful since the introduction of effective drug-eluting stents, and its indications in improving reocclusion rate[44] in coronary bypass grafting is currently insufficient. Therefore its major documented benefits still rest on patients after myocardial infarction. Although the benefits obtained is comparable to that seen after treatment with statins,[44] caution should be adopted in such interpretation by realizing the uncertainties in dietary trials including potentially unaccounted dietary and lifestyle changes. On the other hand, little has been concluded about its use in the primary prevention. Currently a large randomized controlled trial is being conducted in Japan,[55] in which 15000 hypercholesterolaemic subjects free of CAD are randomly given a statin or a statin plus 1.8 g of purified EPA and DHA. The primary endpoint will be the number of major coronary events. It is expected that by the end of this year the trial will be complete and help us understand more the role of omega-3 fatty acids in the primary prevention of CAD.

## Phytoestrogens

Phytoestrogens are a diverse group of compounds found in various plant-derived foods and beverages, exhibiting both oestrogenic and antioestrogenic activities. There are 3 main categories of phytoestrogens, namely isoflavones, lignans, and coumestans (Figure 3). The isoflavones are abundant in soybeans, chick peas,

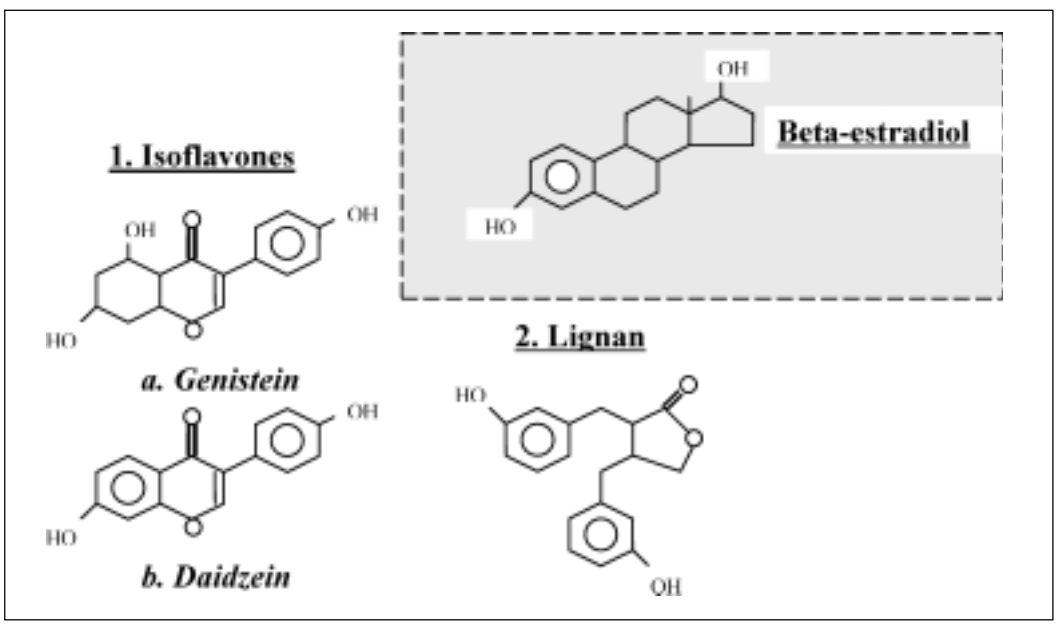


**Figure 3.** *Structure of phytoestrogen molecules: 1: Isoflavones (a. genistein ; b. daidzein) and 2: Lignans. The molecular structure of phytoestrogen resembles that of endogenous estradiol, accounting for its partial estrogen-mimicking biological properties. Its biological activities in vivo, however, are more versatile than simply estrogenic and anti-estrogenic activities. Its anti-oxidant and other properties have yet to be further elucidated.*

clovers and other legumes. Lignans are present as a significant ingredient in cereals and oilseeds such as flaxseed, while coumestans are found in alfalfa and various beans. Among all, isoflavones constitute the most common and available form of phytoestrogen, and of which the 2 most abundant active components being genistein and daidzein. Because of their resemblance to estradiol in structure and function, they appear to exhibit selective estrogenic actions i.e. proestrogenic responses is observed in some tissues while estrogen inhibitory responses in others. The antiestrogenic effects may be due to competitive inhibition at the estrogen receptor, interference with gonadotrophins, inhibition of estrogen synthesis or increased synthesis of estrogen binding proteins.[56-58]

A major dietary source of phytoestrogen is soy, including various forms of food such as soybeans, tofu and soy milk. The concentration of genistein in most soy food materials is about 1 to 2 mg per gram of protein. There is a marked difference in the daily intake of phytoestrogen in Asians as compared to Western population. The typical intake value in many Asian populations with low rates of breast and prostate cancer is 20 to 8 mg per person per day, in contrast to only 1 to 3 mg per person per day in United State.[56]

Isoflavones by themselves are inactive. Its absorption and subsequent action depends on initial conversion by intestinal flora. After absorption, the isoflavones are reconjugated and excreted unchanged in the urine. This allows the body level to be estimated by bioassay either in the serum or urine. Although dietary phytoestrogen metabolism is significantly influenced by intestinal flora, antibiotic use or bowel pathology, measurement of the serum or urinary concentration of its metabolites still serves as a valid means of intake estimation in the population. Most isoflavones are excreted within 48 hours after ingestion and urinary level of isoflavonoids is a good indicator of short-term soy food intake. From a study addressing the correlation of soy food consumption and overnight urinary excretion of isoflavonoids among Chinese women in Shanghai, the urinary assessment correlated well with the soy food intake assessment by food frequency questionnaire not only at the group level but also at the individual level.[59]

Epidemiological studies observed that the incidence of cardiovascular diseases is markedly lower in Asian populations,[57,60] in whom phytoestrogen consumption is abundant. Indeed, not only are cardiovascular diseases but some other diseases including breast cancer, prostate cancer and colorectal cancer also exhibiting similar distribution patterns. The available evidences, collectively from basic science, animal and human research studies, are summarized in Table 4. It is believed that the observed protective effects of phytoestrogen against various diseases share major

**Table 4. Potential effects of phytoestrogens observed in preclinical and clinical studies**

| **Preclinical** | **Clinical** |
|---|---|
| ↓ Cholesterol | ↓ Cholesterol |
| ↓ LDL Oxidation | ↓ LDL oxidation |
| ↑ Antioxidant enzymes | ↓ Perimenopausal hot flushes |
| ↓ Atherosclerotic lesions | ↓ Cancer incidence |
| ↑ Vascular reactivity | ↑ Bone mineral density |
| ↓ Platelet aggregation | ↑ Vascular function |
| ↓ ICAM-1 & VCAM-1 expression | ↓ Blood pressure |
| ↓ Angiogenesis | |
| ↓ Neoplastic proliferation | Side effects observed: |
| ↓ Bone loss | ↑ Breast secretions |
| ↓ Ventricular remodellation | ↑ Breast epithelium proliferation |
| | ↑ Endometrial proliferation |

Adapted and modified from Lissin et al.[58]

pathways as anti-oxidant, anti-angiogenic properties as well as hormonal regulatory properties possessed by the molecule.

A large number of studies had been conducted to investigate the effect of dietary soy protein on the lipid profile (Table 5). Meta-analysis of these studies concluded that a mean intake of 47 g of soy protein daily was associated with a reduction in total plasma cholesterol of 9%, in LDL-C of 13% and in triglycerides of 10%.[61] However, the reduction in cholesterol was directly related to the initial cholesterol level, and no significant change was observed if the initial level was low. The Soy Health Effect Study (SHE) also showed that women with a higher genistein intake had a significantly reduced waist circumference with improved fasting insulin and an increased HDL-C level.[56]

Three mechanisms have been proposed to explain for the hypocholesterolaemic effects of phytoestrogen: 1) stimulates bile secretion and therefore indirectly enhances removal of LDL; 2) phytoestrogen intake induces a free thyroxine surge and thereby a hyperthyroid state which alters the lipid profile; and 3) altered hepatic metabolism with augmented LDL-C and VLDL-C removal by hepatocytes, and such removal stimulates the clearance of cholesterol by upregulating LDL receptors and hence increasing LDL receptor sensitivity. An interesting evidence for the last proposed mechanism arises from an experiment in which LDL-receptor deficient mice have no observed benefit of isoflavone-rich diet intake when simultaneously fed with cholesterol-rich diet, as opposed to the normal mice in which the isoflavone-rich diet exerts a counteracting effect on the high cholesterol intake.[56]

Nonetheless, whether the hypocholesterolaemic effect is possessed by phytoestrogen or other components present in soy protein remain unclear. Meta-analysis on studies specifically investigated the effect of soy-associated isoflavones on cholesterol concentrations have concluded that isoflavone consumption is not related to LDL or HDL cholesterol changes.[62] It is, therefore, possible that the observed hypocholesterolaemic effect related to soy should be accounted by another component.

It is well known that atherosclerosis is initiated by monocytes binding to the endothelium and migrating into the intimal layer to develop into foam cells. The adhesiveness of the endothelial cells is caused by the lipid-induced, oxidant-sensitive transcription of adhesion molecules and chemokines, which stimulates monocyte binding. Since oxidative modification of LDL plays a role in the initial process of atherogenesis, phytoestrogen, by modification of the oxidative process may prevent subsequent parts of pathogenesis.[37,39] Clinical studies have shown that consumption of soy-derived isoflavones by healthy individuals for 2 weeks resulted in an increased oxidation resistance of LDL.[63] Interestingly, the LDL particles isolated from these subjects contained considerable amounts of isoflavones, thus implying alteration of the LDL particles. Furthermore, a biomarker of in vivo lipid peroxidation, 8-epi-prostaglandin F2a was also significantly lowered in plasma by the intake of diets high in isoflavones.[64]

Genistein has been found to exhibit anti-proliferative effects in human cell lines and being capable of inhibiting expression of intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 on human endothelial cells. In addition to being a specific inhibitor of tyrosine kinase, genistein also was found to prevent in vivo thrombogenesis and suppress in vitro platelet aggregation in mice.[56,58]

Preclinical studies in non-human primates have showed that vascular reactivity was favorably influenced by phytoestrogens. There is also observation that genistein and daidzein relax mesenteric arterial rings of rats in a dose-dependent manner.[10,56] There are several clinical studies in humans to investigate the effect of phytoestrogens on endothelial function, however, these studies are limited by small study population and only performed in postmenopausal women.[65-70]

Recently there has been further vigorous discussion on the validity of a cardioprotective role claimed by dietary phytoestrogen. Van der Schouw et al[76] prospectively studied 16165 Dutch women aged between 49 to 70 years old for a median period of 75 months. The results of this study have shown that neither isoflavones nor lignans were associated with decreased cardiovascular risk, although the risk is decreased with increasing lignan intake for ever smokers. However, one major limitation of this study was the generally low

**Table 5. Randomized controlled trials of soy protein & phytoestrogen in relation to cardiovascular health**

| Reference | Population | Intervention | Duration | Outcomes[a] |
|---|---|---|---|---|
| Simons et al 2000[65] | Cross-over study in 20 healthy postmenopausal women | 80 mg isoflavones or placebo daily | 8 weeks | → Blood pressure<br>→ Plasma lipids<br>→ FMD |
| Hermansen et al 2001[71] | Cross-over study in 20 type II diabetic patients | 50 g soy protein (165 mg isoflavones) or placebo (50 g casein) | 6 weeks | ↓ LDL cholesterol<br>↓ Apolipoprotein B100<br>↓ Triglycerides<br>↓ Homocysteine<br>→ HDL cholesterol<br>→ Blood pressure |
| Teede et al 2001[66] | Parallel study in 213 healthy men & postmenopausal women | 40 g soy protein & 118 mg isoflavones or casein placebo | 3 months | ↓ LDL/HDL ratio<br>↓ Triglycerides<br>Adverse effects:<br>↑ Lp(a) lipoprotein<br>↓ FMD |
| Lichtenstein et al 2002[72] | Cross-over study in 42 subjects aged above 50 years with LDL-cholesterol >3.36 mmol/L | Four experimental diets: soy protein depleted or enriched in isoflavones (50 mg/ 4.2MJ), animal protein with or without added isoflavones; daily | 6 weeks | Soy protein:<br>↓ Total & LDL cholesterol level in patients with ≥4.14 mmol/L<br>Isoflavone:<br>No significant effect observed |
| Dewell et al 2002[73] | Parallel study in 36 moderately hypercholesterolaemic postmenopausal women | 150 mg phytoestrogenor placebo daily | 6 months | → Lipid profile |
| Squadrito et al 2003[67] | Parallel study in 79 healthy postmenopausal women | Estrogen/progestin, or genistein 54 mg or placebo daily | 1 year | ↑ Nitrate/nitrite level<br>↓ Endothelin-1<br>↑ FMD 5.5% |
| Teede et al 2003[74] | Cross-over study in 46 healthy men & 34 women | 80 mg isoflavones enriched in biochanin or formononetin, or placebo | 6 weeks | ↑ Systemic arterial compliance<br>↓ cPWV<br>→ FMD<br>→ Blood pressure |
| Steinberg et al 2003[68] | Cross-over study in 28 postmenopausal women | Three 25 g protein products respectively with 107, 2 and 0 mg total isoflavones daily | 6 weeks | ↑ FMD<br>→ Endothelial markers |
| Lissin et al 2004[69] | Parallel study in 40 postmenopausal women | 90 mg isoflavones or placebo daily | 6 weeks | ↑ Vascular reactivity to nitrogycerine<br>→ FMD<br>→ Lipid profile |
| Kreijkamp-Kaspers et al 2005[70] | Parallel study in 202 postmenopausal women aged 60-75 | Soy protein containing 99 mg isoflavones or milk protein placebo daily | 1 year | Equol producers:<br>↓ Blood pressure<br>↑ Endothelial function<br>Equol nonproducers:<br>↑ Blood pressure<br>↓ Endothelial function |
| He et al 2005[75] | Parallel study in 302 Chinese adults aged between 35 to 64 | Soybean cookies containing 40g of either soybean protein or complex carbohydrate daily | 12 weeks | ↓ 3 to 4 mmHg systolic & diastolic blood pressure |

[a] FMD: Flow-mediated dilatation; cPWV: Central pulse wave velocity.

intake of isoflavones in the population.[77] The median daily intake of isoflavones was only 0.369 mg. Even in the 4th quartile, the total daily isoflavone intake was only 0.541 mg, which is significantly lower than in the Asian populations. It is possible that the intake is too low to exert a significant protective effect. The study also did not provide a serum or urine quantification of phytoestrogen level to confirm the dietary intake. Therefore we should be cautious on such interpretation. Further prospective randomized controlled trials studies are needed to provide further verification.

## Conclusions

Epidemiological observation studies on selected dietary approaches, such as the Mediterranean diet, have been shown to be associated with a reduced incidence of CAD. However, very limited clinical evidences are available to support their use for primary prevention of cardiovascular diseases. Among these dietary approaches, only Mediterranean diet has been demonstrated to be effective for secondary prevention of cardiovascular diseases. Related clinical trials on diet conducted so far are limited by uncontrolled caloric intake and concurrent changes in alternative food consumption. Before further studies are performed to give more informative guidance, a diet rich in fresh fruits and vegetables but restricted for high GI carbohydrates, with polyunsaturated fat intake from plant oil and fish is generally advisable and mostly consistent with the current evidence for heart health. An individualized approach and the importance of holistic lifestyle commitments including regular exercise should be emphasized.

Most nutritional supplements, on the other hand, either prove inefficacious in conferring cardiovascular benefits, or that the efficacy is conflicting. Some of them may actually be harmful if taken regularly. Physicians should therefore be cautious in advising on and prescribing these supplements. Phytoestrogen, for instance, represents a recently focused branch of nutritional substances with potentially cardioprotective implications. Ample supportive experimental data exist but clinical studies are negative in general. Its recommendations will depend upon further randomized controlled trials.

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