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Guest Editorial

Beta-blockers: A Second Rate Treatment for Hypertension?

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Hypertension is a major risk factor for stroke and myocardial infarction. Lowering blood pressure by 5-6 mmHg reduces the stroke risk by 38%.[1] It is astonishing that the treatment of hypertension is so beneficial when the efficacy of currently available antihypertensive drugs is so modest. Thus, any drug, which lowers blood pressure and is safe, is approved for clinical use. In the last decade, large clinical trials have been conducted to compare antihypertensive drugs in terms of cardiovascular outcome.[2,3] One of the latest trials was the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the results of the blood pressure lowering arm of which have recently been reported at the American College of Cardiology Annual Scientific Session.[4] The database is not complete yet, but the preliminary results already show that the amlodipine-perindopril arm (new drugs) had better outcomes than the diuretic-beta-blocker arm (old drugs). Furthermore, there were more new cases of diabetes in the latter arm.

The results of ASCOT were unexpected, because previous trials of old versus new drugs had been a tie.[5-7] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[8] diuretics performed as well as amlodipine and lisinopril, but because thiazide diuretics have been in use for a long time and are economical, they are promoted as first line treatment in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).[9] However, beta-blockers are not advocated as first line treatment in JNC7. In the British guidelines, there are explicit reservations regarding beta-blockers.[10] In older trials on hypertension, beta-blockers were used together with thiazide diuretics and so took a share of the credit for the benefits shown.[1] On their own, they are less than impressive.[11] In the Medical Research Council trial of treatment of hypertension in older adults, beta-blockers were no better than placebo and significantly inferior to diuretics.[12] In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), atenolol was inferior to losartan with regard to stroke, although it was non-significantly better than losartan in terms of myocardial infarction.[13] A recent meta-analysis showed that atenolol performs consistently less well than other antihypertensive drugs in clinical trials.[14]

ASCOT was an unequal race between old war-horses and young thoroughbreds. Diuretics and beta-blockers need to be used at low doses, limiting their blood pressure lowering effect. These drugs also worsen the metabolic profile whereas angiotensin-converting enzyme inhibition prevents diabetes.[15] Amlodipine is a very efficacious antihypertensive agent.[16,17] Small differences in blood pressure control can be translated to significant differences in clinical outcome, as in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.[18,19] Amlodipine also has an anti-atherosclerotic effect in carotid and coronary arteries.[20,21]

Beta-blockers remain valuable in the treatment of angina pectoris and myocardial infarction, and their use in heart failure clearly reduces mortality.[22] They are contraindicated in asthma and peripheral vascular

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disease. In the light of the latest evidence, the use of a beta-blocker should not be a reflex but a carefully considered action. The American and World Health Organization guidelines may require revision,[9,23] whereas the European guidelines characteristically give equal weight to each antihypertensive drug class.[24] The British guidelines hold up rather well.[10] The British Hypertension Society, adopting the Cambridge ABCD rule, proposes that beta-blockers are less suitable as first-line treatment in the elderly.[25] I would not discard them for the moment, not least because they are surprisingly the best tolerated antihypertensive drug class apart from angiotensin receptor blockers.[26] The majority of patients require a number of drugs to reach current blood pressure targets (140/90 mmHg and lower targets for patients with diabetes or nephropathy).[9,10,23,24] Beta-blockers may therefore be one of the drugs used to attain good blood pressure control.[27] Drug companies are keen to emphasise and exploit small differences between drugs, but these pale into insignificance when compared to the paramount importance of good blood pressure control. Beta-blockers are out of favour for hypertension for the moment, but the full results of ASCOT are still awaited. The pendulum may swing this way and that way from time to time, but it will finally come to rest in the middle.

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Exercise Habit of Cardiac Patients after Phase II Cardiac Rehabilitation Programme

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MAK ET AL.: ***Exercise Habit of Cardiac Patients after Phase II Cardiac Rehabilitation Programme. Objectives:*** *To determine the exercise habit of patients who completed Phase II cardiac rehabilitation programme (CRP) from July 2002 to October 2003.* ***Methods:*** *Phone survey was conducted with patients who self-reported their exercise pattern. Type, frequency, duration, and intensity of exercise; exercise tolerance (ET) in terms of flight of stairs (FOS) achieved and walking distance on level ground, and pre-programme exercise habit were analysed.* ***Results:*** *Among 120 Phase II graduates, 107 patients responded to the survey. Ninety-five patients (70 males), aged 45-82, reported they did exercise weekly. Forty-six patients (48.4%) did not exercise regularly beforehand. Walking was the most common exercise (66.3%). Light and moderate to vigorous-intensity exercises were performed by 47% and 53% of patients respectively. Exercise <3 times/week or spent <30 minutes/session was revealed in 27% of patients. Frequency and duration of exercise were not statistically different between male and female patients. However, patients ≥65 years did exercise more often than their younger counterparts (p= 0.018). Regarding ET, 60% and 63% of patients reported that they could walk for >1 hour on level ground and climb ≥6 FOS at a time respectively.* ***Conclusions:*** *Most patients (88.8%) could achieve regular exercise habit after completion of Phase II CRP. However, more than 25% of patients did not practice exercise accordingly to the exercise guidelines. Education and counselling in long-term maintenance of exercise with appropriate frequency, duration and intensity should be emphasised. (J HK Coll Cardiol 2005;13:4-9)*

Cardiac rehabilitation, exercise

摘要

目的：目的在於評價從2002年7月至2003年10月間，完成II期心臟康復計劃患者的運動習慣。**方法：**對於那些每日自我報告運動方式的病人，採用電話問訊的方式進行資料採集。收集運動的方式、頻率、持續時間和強度，並且分析階梯攀登的運動耐受性，平地步行的距離和計劃前的運動習慣。**結果：**在120名完成II期康復計劃的患者中，有107人對調查做了恢復。95位患者（其中男性70位），年齡45-82歲，報告他們每周參加運動。46位患者（48.4%）在這之前不定期鍛煉。步行是最常見的運動方式（66.3%）。47%和53%的患者分別採用了輕度和中度強度的運動。27%的患者每周運動次數小於3次，或者每次運動小於30分鐘。運動的頻率和持續時間在男女患者間不存在統計學差別。然而，年齡大於65歲的患者相比年輕的患者更多地參加運動（p = 0.018）。至於運動耐受性方面，有60%和63%的患者報告說，他們能夠分別在平地步行超過1小時和攀登階梯≥6個單位。**結論：**絕大多數的患者（88.8%）能夠在II期心臟康復計劃後實現經常鍛煉。然而，有超過25%的患者卻由於運動指導缺乏而未參加鍛煉。關於運動的適合頻率、持續時間和強度，其長期教育和諮詢是格外需要強調的。

關鍵詞：心臟康復　運動

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Introduction

Regular exercise is one of the risk-reduction interventions in cardiac rehabilitation.[1] It improves atherosclerotic risk factors, reduces cardiac mortality, and decreases symptoms development in patients with

coronary artery disease (CAD).[2-4] On completion of Phase II training, exercise prescriptions and the importance of continuing regular exercise are given to patients by physiotherapists. The purpose of this study was to determine the exercise habit of cardiac patients following their completion of Phase II cardiac rehabilitation programme (CRP).

Methods

Subjects

Cardiac patients who completed Phase II CRP in United Christian Hospital during the period from July 2002 to October 2003 were included in this study.

Outcome Measures

Parameters including type, frequency, duration, and intensity of exercise performed by patients, exercise tolerance (ET) in terms of flights of stairs (FOS) achieved and walking distance on level ground, and exercise habit before Phase II training were used to measured patients' exercise pattern. In evaluation of FOS achieved, a fight of stairs was regarded as 10 steps.[5]

Survey Form

The phone survey was conducted in early March 2004. Questionnaire consisted of eight questions was used to explore and record patients' exercise pattern (Figure 1). Patients self-reported their current exercise pattern. Their replies were then categorized and analysed accordingly. Types of exercise performed by patients were classified into light (<3 metabolic equivalents, METs), moderate (3-6 METs), and vigorous intensity (>6 METs).[6]

Results

One hundred and twenty patients completed Phase II CRP during the period from July 2002 to

Name：_____ MRN: _____ Sex / age: ____/____

Q1. Do you exercise after Phase II CRP? Yes / No, reasons:_____

(If yes, go to Q2.)

Q2. How often do you exercise every week? _____times/week

Q3. What type of exercises do you do? _____(major)

_____(minor)

Q4. What is the duration for each exercise session? _____(minutes)

Q5. How far can you walk? _____(hours)

Q6. Can you do stair climbing? Yes / No (If no, go to Q8.)

Q7. How many flights of stairs can you take? _____ (FOS)

(For those who can manage stairs)

Q8. Did you exercise more than 3 times per week before participate in Phase II? Yes/No

Figure 1. *Survey form for assessment of patients' exercise habit after completion of Phase II CRP.*

October 2003. There were 86 males and 34 females, their age ranged from 43 to 82 years old. By the time of the study, they were discharged five to twenty months from Phase II training. Thirteen patients' data were not available due to death in four, refusal to study in one, and inability to contact in eight patients.

Non-Exercise Group

Out of 107 patients who responded to the survey, 12 patients (11.2%) did not exercise. There were 6 males and 6 females, age ranged from 43 to 80 years. Major barriers including injuries and pain over body parts, recent medical events, time constraints, and forgot own exercise prescription were reported in five, three, three, and one patients respectively.

Exercise Group

Ninety-five patients (88.8%) reported that they did exercise after Phase II training. There were 70 males and 25 females, their mean age was 65.1±9.0 (range 45-82) years. Fifty-four patients (56.8%) were aged over 65. Among 95 patients, 48.4% of patients developed exercise habit following Phase II CRP.

Patients' Exercise Pattern

1. Types and Intensity

Walking was the most common type of exercise practiced by 66.3% of patients, followed by Chinese Wushu for example Tai Chi and Qigong, and stretching by 24.2%, and 11.6% of patients. Other types of exercise including swimming, playing ball games, cycling and hiking were also done by patients (Figure 2). Out of those 95 patients, three patients did exercise at community or sports centres. All patients created their own exercise programme. Fifty-five patients (47%) performed light-intensity exercises, the rest (53%) worked out at moderate to vigorous level (Figure 3).

2. Frequency and Duration

Thirteen patients (13.7%) did exercise <3 times/ week, while 61 patients (64.2%) of patients did exercise almost everyday (Figure 4). Twenty patients (21.1%) spent <30 minutes/sessions, while 33 patients (34.7%) spent ≥60 minutes on each exercise session (Figure 5). Furthermore, 26 patients (27.4%) did exercise less than three times per week or spent less than 30 minutes per

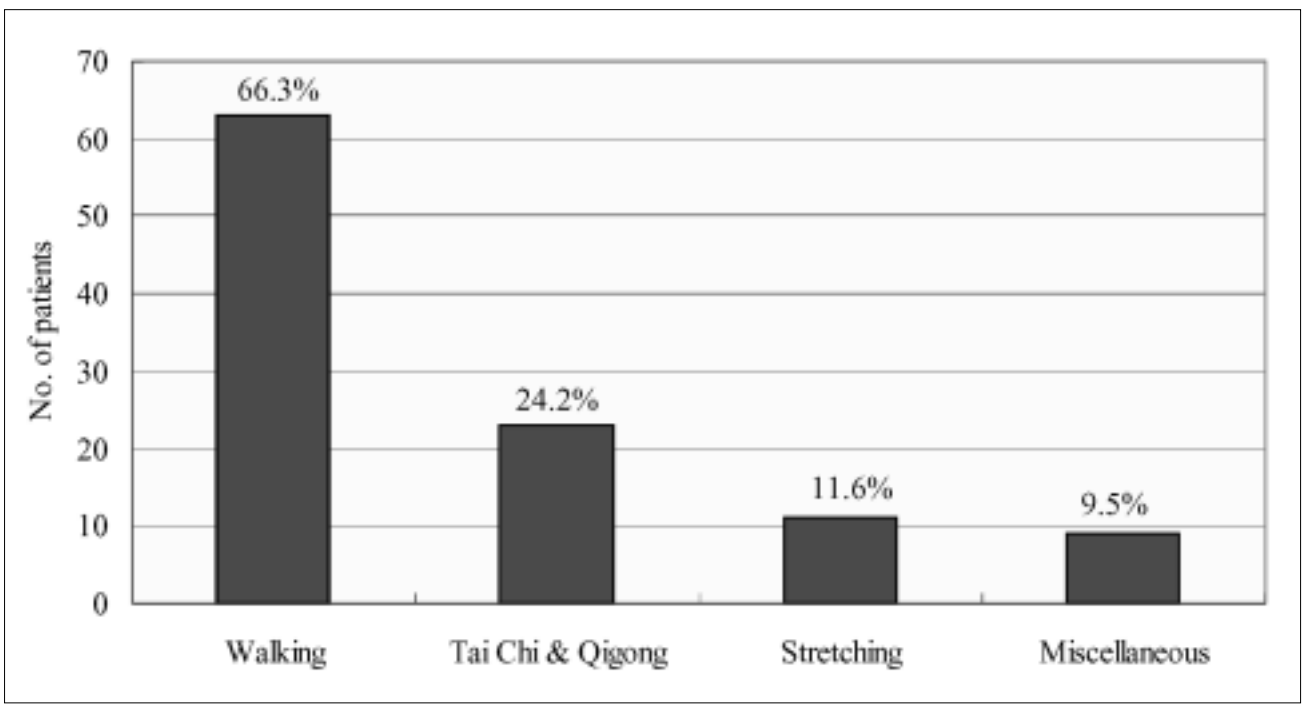

Figure 2. *Types of exercise performed.*

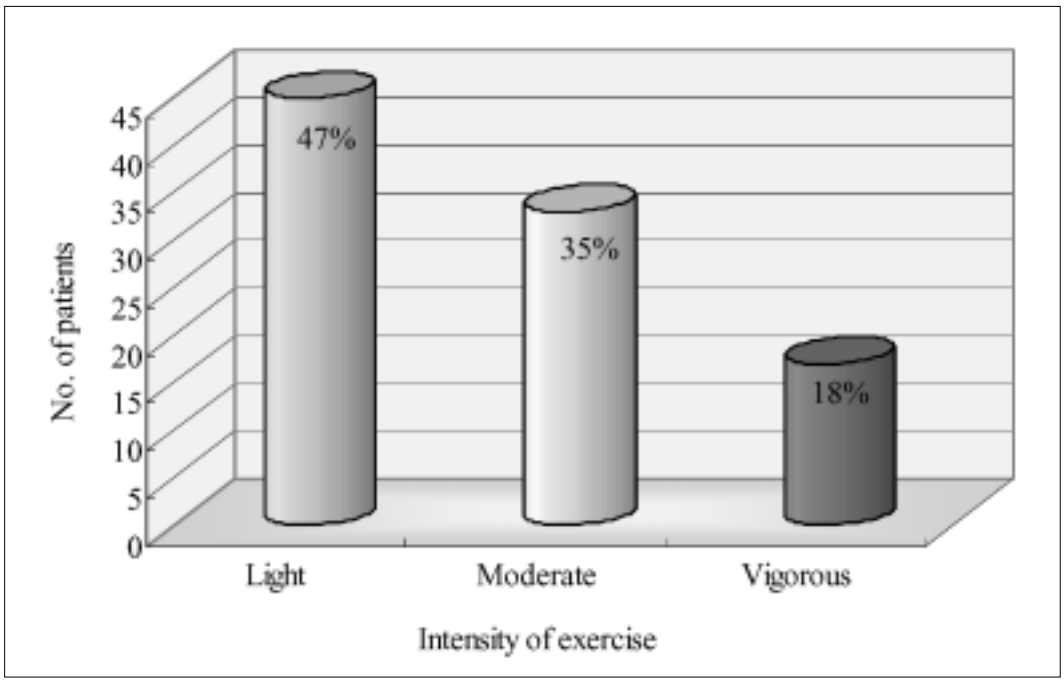

Figure 3. *Intensity of exercise.*

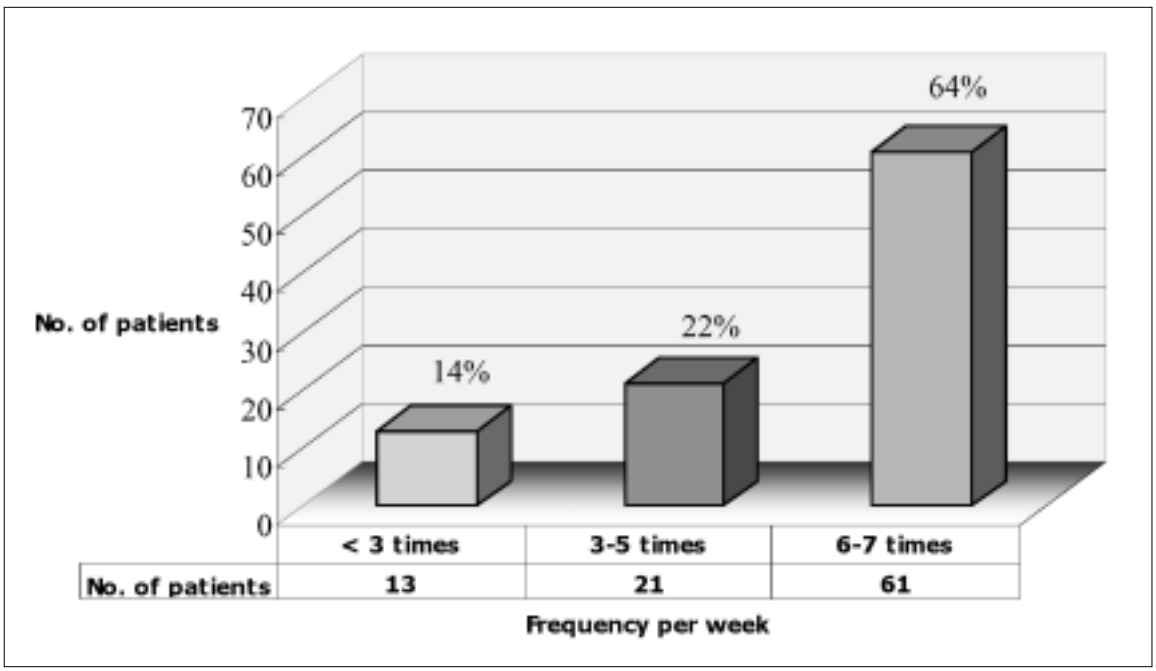

Figure 4. *Frequency of exercise.*

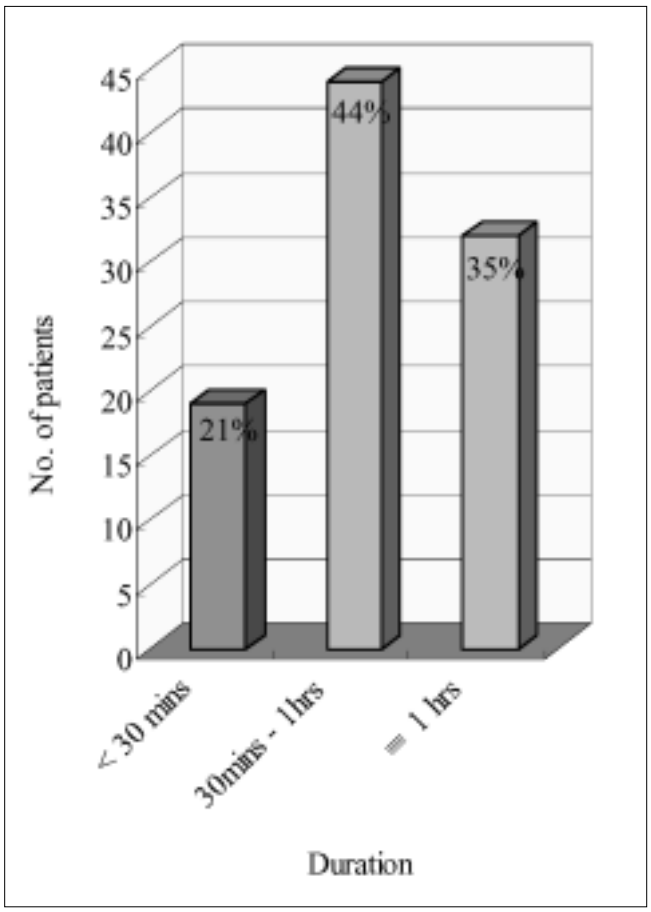

Figure 5. *Duration of exercise.*

exercise session. There were not statistically different in frequency and duration of exercise between male and female patients. However, patients ≥65 years exercise more frequent than their younger counterparts did (p=0.018).

3. Exercise Tolerance

Sixty percent of patients reported that they could walk for more than an hour on level ground. Sixty-three percent of patients reported that they could climb six or more FOS, which implied ≥60 steps of stairs, at a time.

Discussions

According to guidelines from the Centers for Disease Control and Prevention and the American College of Sports Medicine, patients are recommended to do at least 30 minutes of moderate-intensity (≥3 METs) exercise on most, and preferably all, days of the week.[1,4,7] Furthermore, to maximize the benefits of cardiac rehabilitation, long-term maintenance of regular moderate-intensity exercise for least 12 weeks is necessary.

Although the benefits of exercise are acknowledged, compliance to the recommendations is difficult.[8] In USA, less than 25% of Americans could achieve the recommended level of exercise.[4] In our study, 47%, 14%, and 21% of patients had less than the recommended level of intensity, frequency, and duration during exercising. Long-term maintenance of exercise is not easy as well, especially when supervision is withdrawn.[8] Community-based exercise classes provide regular, structured and supervised training programme. However, only 3% of patients in the study worked out at fitness centers. Scottish Intercollegiate Guidelines Network (2002) also indicated that there is no restriction on the nature of exercise performed by patient as long as patients adhere to the recommendation.[8] Therefore, periodically review with patients their exercise pattern and provide education and counseling is essential to support patients' adherence to do exercise after completion of Phase II CRP.[3]

Tai Chi and Qigong was the second most common type of exercise (24.2%) performed by patients. It is also becoming more popular in United States. They are Chinese exercise practice involving gentle movements of body as well as training of body, breath, voice and mind.[9] According to Ainsworth (2000), they were classified as moderate-intensity (3 METs) aerobic exercise.[6,9] Studies had documented their benefits in many areas including elders, arthritis patients, patients with cardiovascular disease, and others with chronic illness.[9] Therefore, the exercise could be promoted to cardiac patients with associated illness.

Metabolic equivalent (MET) is an absolute scale in measuring the intensity of exercise. Its classification was based on the physical effort of healthy, middle-aged adults. Lee et al. (2003) suggested that individual fitness levels should be

considered when "moderate-" intensity exercise were recommended.[2,3,10] In our study, more than one-half of patients were aged over 65 years, and 47% of patients performed light intensity exercise. During review of their exercise pattern, elderly patients did exercise at light-intensity might already accomplished cardiac protection purpose. It is therefore, necessary to consider patients' physical fitness and tailored accordingly.

Sedentary lifestyles in cardiac patients should be avoided. Findings indicated that even some form of exercise provide certain benefits than non-exercise group.[11] For patients who did not exercise, their barriers should be explored. Health care professionals should discuss the benefits, risks, and opportunities about exercise with them.[8] In situation when patients' medical conditions limited them from doing exercise, medical treatment to stabilize their conditions should be given. Their exercise recommendation should be revised and customized to meet their conditions.[12]

Conclusions

Most of the patients (88.8%) could achieve regular exercise habit after completion of Phase II CRP. However, more than 25% of patients did not practice exercise accordingly to the exercise guidelines. Education and counselling in long-term maintenance of exercise with appropriate frequency, duration and intensity should be emphasised.

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Quality of Life in Patients with Atrial Fibrillation

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SIN ET AL.: ***Quality of Life in Patients with Atrial Fibrillation.*** *Atrial fibrillation (AF) is one of the most common symptomatic cardiac arrhythmia and is associated with substantial complications and health care cost. Although AF is not an immediately life threatening disease, it is associated with significant symptoms, and thus impairment of quality of life (QoL). Therefore, one of the major assessments for treatment outcome in AF patients is improvement of QoL. Current available data do suggest that patients with AF have markedly impairment of QoL compared to healthy controls and patients with other cardiovascular diseases. In the majority of AF patients, rate or rhythm control appears to provide similar benefit on QoL. However, in highly symptomatic AF patients, successful nonpharmacological rhythm-control might yield the largest improvement in QoL. Future studies are required to compare QoL in different patient populations, different types of AF and different therapeutic approaches in patients with AF. Furthermore, the development and validation of a more disease-specific QoL instrument for AF can improve the measurement of health status in patients with AF. (J HK Coll Cardiol 2005;13:10-15)*

Atrial fibrillation, quality of life

摘要

房顫是最常見的有症狀的心律失常，它還伴隨著併發症的發生和健康照料費用的開支。雖然房顫並不是迅速威脅生命的疾病，但是它往往產生明顯的症狀，由此而影響生活質量。因此，對於房顫病人治療的一個重要評價指標就是提高生活質量。當前的資料顯示，相比其他健康狀況控制良好的心血管疾病患者，房顫病人的生活治療受到了明顯的損害。在大多數房顫的病人中，心律的控制意味著能夠爲生活質量提供相應的益處。然而在有嚴重症狀的房顫病人中，成功的非藥物方法的心律控制能夠最大限度地提高生活質量。進一步的研究要求我們比對不同病人人群，不同房顫類型和不同治療方式下的生活質量。此外對於房顫，更加病症專一的生活質量評價手段的發展和確立，能夠提高房顫病人健康狀況測定。

關鍵詞：房顫　生活質量

Introduction

Atrial fibrillation (AF) is one of the most common symptomatic cardiac arrhythmia and is associated with substantial complications and health care cost. Epidemiology studies have shown a prevalence of 0.5% to 1% for AF in the general population.[1,2] The prevalence of AF increases with age with less than 1% in those under 60 years of age and greater than 6% in those aged 80 years or older.[1] In Hong Kong, AF occurs in 1.3% of healthy adults aged >65 years.[3] In United States, the median age of subjects with AF is 75 years, with 70% between the ages of 65 and 85 years.[4] Furthermore, Framingham study have demonstrated that AF is more common in men and has a 1.5-fold greater risk of developing AF than women after adjustment for age and predisposing conditions.[2]

AF is frequently associated with the presence of underlying cardiovascular disorders. Prior studies in Hong Kong had shown that hypertension (29%),

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artherosclerotic cardiovascular disease (25%) and chronic rheumatic heart diseases (17%) accounted for over 70% of the patients admitted into hospital with AF.[5] Furthermore, heart failure is closely associated with AF. In patients with heart failure, the prevalence of AF increases from <10% in those with New York Heart Association (NYHA) functional class I to approximately 50% in those with functional class IV.[6] Lone AF describes situations in which no underlying or detectable causes for AF could be identified, and is reported to occur in 12-30% of patients with AF.[7-9]

The total mortality rate, which is largely due to stroke, is approximately doubled in patients with AF compared with patients in normal sinus rhythm.[10,11] In patients with rheumatic heart disease and AF, stroke risk was increased 17-fold compared to age-matched controls.[12] The rate of ischemic stroke among patients with non-rheumatic AF averages 5% per year, which is 2 to 7 times the rate for people without AF.[10] Furthermore, those patients with advancing age, prior stroke, hypertension, diabetes or congestive heart failure have a higher risk of stroke.[11]

As discussed above, considerable studies have been performed to address the epidemiology and clinical consequences of AF. Therefore, studies on the efficacy of therapy in AF have been predominantly assessed by morbidity and mortality measures. Although AF is not an immediately life threatening disease, it is associated with significant symptoms. Patients with AF have symptoms that are highly likely attributable to the arrhythmia itself, rather than accompanying cardiovascular conditions. Therefore, one of the major purposes for treatment of patients with AF is to relieve symptoms and to improve quality of life (QoL). As a recent, more interest has been developed on the assessment of patient related issues, such as improvement of symptoms and QoL, as objectives in treating AF.[13] This article reviews currently available data on the assessment of QoL in patients with AF.

Definition of QoL

Since 1947, when the World Health Organization defined health as being not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being, the issue of QoL has become steadily more important in health care practice and research.[14] The World Health Organisation Quality of Life Group defined QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[15] It is a broad range of concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment.

QoL is a multidimensional concept and no universal definition exists. Campbell et al notions of QoL encompass domains such as housing, employment, standard of living and marriage, etc.[16] Economic, political, cultural, and spiritual factors may affect overall QoL, but are generally not considered to fall under the purview of physicians and health care systems.[17] In the literature, the terms health-related QoL, QoL, health status and functional status are often used interchangeably. QoL is a broader concept while health-related QoL only includes aspects related to health only. Five health concepts are inherent in health-related QoL definition: physical health, mental health, social functioning, physical and general well-being.[18] Health-related QoL can be conceptualised as the physical, psychological, and social domains of health which are influenced by a person's perceptions experiences, beliefs, expectations, and perceptions.[19] The distinction between health status and QoL is that health status refers to the actual state of health but QoL measures the perceived impact of health on life.[20] Health status can be assessed by objective as well as subjective methods but QoL is always subjective. Functional status refers to the physical, emotional and social consequences of the disease process. It often includes measures that assess performance of activities of daily living, such as walking, eating or interacting with family.[21]

Assessment of QoL in Patients with AF

Measurement of QoL is particularly relevant to the management of AF as the one of the major goal of

treatment is to relieve symptoms and improve QoL in this chronic condition. There are several purposes to evaluate QoL in patients with AF: 1) to select patients for various treatment; 2) to determine the choice of treatment; 3) to monitor patients progress; 4) to assess the impact of complications; and 5) to use as an outcome measure in research studies and clinical trials.

The instruments available to measure QoL can be divided into either 1) generic instruments or 2) disease-specific instruments. Generic instruments are usually broader measures of health status. They are used in the general population to assess a wide range of domains and can be applied to a variety of health states, conditions, and diseases. They are usually not specific to any particular disease and therefore are useful for making comparisons between disease states. The Medical Outcomes Study Short Form Health Survey (SF-36) is currently the most widely validated generic instrument.[22-25] A generic instrument is often used in combination with a disease-specific instrument which is more sensitive to detect symptoms-related changes. Disease-specific instruments focus on the domains most relevant to the disease or condition under study and on the characteristics of patients in whom the conditions is most prevalent. The Symptom Checklist: Frequency and Severity (SCL) is a disease-specific instrument developed for patients with cardiac arrhythmias.[26] However, there is no disease specific QoL for patients with AF.

The Medical Outcomes Study Short Form Health Survey (SF-36)

The SF-36 is a widely validated generic measure that has been used in estimating disease burden, such as in conditions of arthritis, back pain, cancer, and cardiovascular disease. It is useful for making comparison with the general population. SF-36 is a generic health scale with eight subscales of health dimensions: physical function, role limitations due to physical problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. The scores in each of the eight subscales are standardized from 0 to 100, and a higher scale scores indicates better QoL. The SF-36 is commonly used because there is a lot of evidence to support its conceptual base, validity, reliability, psychometric properties, sensitivity and responsiveness in many different populations and patient groups.[22-25] Internal consistency reliability coefficients (Cronbach' alpha) on all scales of the SF-36 exceed alpha of 0.8, except for social functioning with alpha of 0.76.[23] The use of the SF-36 survey was validated across 24 diverse patient groups and reported reliability coefficients with a range of 0.65 to 0.94 across.[24] The Chinese (HK) version of the SF-36 health survey was the only health-related QoL measure that has been both validated and normed on Chinese adults in Hong Kong.[25,27]

Symptom Checklist: Frequency and Severity (SCL)

The symptom checklist: frequency and severity was specifically developed for patients with cardiac arrhythmias.[26] The checklist comprises 16 items that are specific for arrhythmias, such as palpitations, dyspnoea, dizziness, exercise intolerance, chest discomfort and syncope, etc. Both the frequency and severity of symptoms related to the arrhythmias are quantified. Frequency is quantified from 0-4: "0" for "Never"; "1" for "Rarely"; "2" for "Sometimes"; "3" for "Often" and "4" for "Always". Severity is quantified from 0-3: "1" for "Mild", "2" for "Moderate" and "3" for "Extreme". The range of possible scores is 0-64 for frequency and 0-48 for severity. Higher scores reflect more symptomatic individuals.

The SCL is a disease-specific measure. Disease-specific measures can be more responsive to changes in patients' health because they highlight more relevant manifestations of the illness and tailor their response categories to a more relevant range of function than generic measures.[28] Berkowitsch et al investigated the effects of catheter ablation on QoL in 60 patients with AF, and analysed the dynamics of SCL and SF-36 parameters.[29] The results of this study showed that SCL is a more specific instrument for a measurement of the procedure success or failure than SF-36.

QoL in Patients with AF

Table 1 summarised the clinical studies on QoL in patients with AF. In these studies, both patients with paroxymal and chronic AF were included. Four studies have compared the QoL in AF patients with a control group[30-32] or the general population.[33] The results of these studies have consistently demonstrated that patients with paroxysmal and chronic AF,[30-32] silent AF[32] and newly diagnosed AF[33] have significantly poorer QoL than control or general population as determined by SF-36. Furthermore, AF patients had significantly impairment of QoL as compared to patients with coronary artery disease and similar to patients with heart failure.[30] Among patients with AF, female patients reported significantly poorer physical and functional health compared to male patients.[34] In the AFFIRM Study, baseline SF-36 scores and total QoL index scores were also lower in women and patients older than 65 years old.[35] Furthermore, patients with paroxysmal AF who reported frequency arrhythmia recurrence had more impairment of QoL compared to patients with persistent and permanent AF.[36] In patients with persistent and permanent AF, their clinical courses

Table 1. Clinical Studies on QoL in Patients with AF

Reference	Patients (mean age, years)	Types of AF	Objectives	QoL Instruments	Main Findings
Dorian, et al, 2000[30]	152 paroxysmal AF patients (52±12) vs. 47 controls (54±14) vs. 69 patients with coronary artery diseases	Paroxysmal AF	Assess the impact of paroxysmal PAF on QoL vs. control and patients with other cardiovascular disease	SF-36, SCL, Specific activity, Illness intrusiveness, University of Toronto AF severity Scales	- Patients with paroxysmal AF reported significantly impaired QoL compared to control and patients with percutaneous coronary intervention, but was similar to patients with heart failure or postinfarction.
van den Berg, et al, 2001[31]	73 paroxysmal AF (54±13) vs. 180 age- and sex-matched controls	Paroxysmal AF	To assess the impact of AF on QoL, and to determine the predictors of QoL in AF patients	SF-36	- AF patients had impaired QoL in all SF-36 subscales except the pain subscale. - Symptoms and autonomic function were important predictors of QoL.
Savelieva, et al, 2001[32]	154 AF patients (58±12) vs. 49 controls	Chronic AF-40% Paroxysmal AF-60%	QoL in symptomatic AF patients were compared with silent AF patients and controls	SF-36, SCL, Modified Goldman specific activity scale, illness intrusive ratings	- Impaired QoL in all AF patients compared to control group. - In patients with silent AF, most SF-36 scale scores did not differ much with normal subjects, but the perception of general health and the rating of global life satisfaction was poorer.
Kang, et al, 2004[33]	81 patients with AF <3 months (mean age: 67)	Newly diagnosed AF	Compared QoL in patients newly diagnosed with AF vs. general US population	SF-36, SCL	- Impaired QoL in patients with newly diagnosed with AF vs. general population. - Frequency and severity of symptoms inversely related to QoL.
Paquette, et al, 2000[34]	170 AF patients: 62 female (68±9) vs. 108 male (62±1)	Chronic and paroxysmal AF	Compared QoL in male vs. female AF patients	SF-36, SCL, Duke Activity Status Index, University of Toronto Atrial Fibrillation Severity Scale	- Female AF patients had more QoL impairment than male AF patients.

are more predictable with stable ventricular rate, and have less impairment in QoL than patients with paroxysmal AF.[37] However, in patients with paroxysmal AF, the severity and frequency of AF episodes were not predictive of QoL.[30,31]

Effect of Therapeutic Intervention on QoL in Patients with AF

In regard to the treatment of AF, successful restoration and maintenance of sinus rhythm are conceptually expected to improve QoL, reduce the morbidity and mortality. However, recent randomized trials have failed to show any superiority of rhythm control strategy, primarily pharmacological over rate control plus anticoagulation strategy in term of quality of life, stroke and mortality.[38-41] In 716 patients included in the AFFIRM QoL substudy,[42] there were no significant difference in QoL score between patients assigned to rate- and rhythm-control at all time points. Furthermore, QoL scores improved in both group with treatment, and were similar whether the actual rhythm was sinus or AF.

The equivalent status of the two therapeutic strategies may not be applicable to all patients with AF. In these studies,[38-41] the majority of patients were elderly with relatively mild symptoms, had multiple risk factors for stroke, but with only a small proportion with severe heart failure. Attempts to improve QoL by restoring sinus rhythm in these AF patients might not be successful.[42] There are different subsets of patients, both young and old, who are candidates for maintenance of sinus rhythm,[43] and may benefit from nonpharmacological approaches including catheter ablation,[44,45] permanent cardiac pacing[46,47] and surgical procedure alone[48] or in combination, in the prevention of AF. In highly symptomatic AF patients, these current available literatures do suggest that these nonpharmacological provide the largest improvement in QoL. However, the majority of studies on the effect of nonpharmacological therapies on QoL in AF patients are limited by small sample size, uncontrolled studies without a control group on medical therapy alone, relatively short duration of follow-up and use of non-validated QoL instruments.

Conclusion

Assessment of QoL has become an important clinical outcome measures in management of patients with AF. Current available data do suggest that patients with AF have markedly impairment of QoL compared to healthy controls and patients with other cardiovascular diseases. In the majority of AF patients, rate or rhythm control appears to provide similar benefit on QoL. However, in highly symptomatic AF patients, successful nonpharmacological rhythm-control might yield the largest improvement in QoL. Future studies are required to compare QoL in different patient populations, different types of AF and different therapeutic approaches in patients with AF. Furthermore, the development and validation of a more disease-specific QoL instrument for AF can improve the measurement of health status in patients with AF.

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Thyrotoxic Heart Disease

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SIU ET AL.: ***Thyrotoxic Heart Disease.*** *The close link between the thyroid gland and the heart has been well recognized since the first description of thyrotoxicosis in nearly 200 years ago. Despite this well known association, there have been only a few population based studies performed on thyrotoxic heart disease except thyrotoxic atrial fibrillation. Even so, there has not been any consensus for the definition for "thyrotoxic heart disease". For other cardiac manifestations of thyrotoxicosis including thyrotoxic cardiomyopathy and thyrotoxic pulmonary hypertension, only occasion case reports can be found in the current medical literatures. Their natural history, clinical course and outcomes are largely unknown. On the other hands, there is an enlarging body of evidence suggesting a direct pathogenic role of thyrotoxicosis per se as the sole cause of these thyrotoxic heart diseases. In this review, we briefly discuss the three cardiac consequences of thyrotoxicosis, namely atrial fibrillation, congestive cardiac failure and pulmonary hypertension. (J HK Coll Cardiol 2005;13:16-20)*

Atrial fibrillation, cardiac failure, thyrotoxicosis

摘要

自從近２００年前第一次描述甲狀腺功能亢進以來，甲狀腺疾病和心臟疾病之間的密切關係已經得到了充分的認識。儘管這一關係已經熟知，但是除了甲狀腺功能亢進的房顫外，只有很少人研究甲狀腺功能亢進的心臟疾病。甚至直到今日對於“甲狀腺功能亢進的心臟疾病”還未有統一的定義。關於其他的甲狀腺功能亢進心臟病的表現，包括甲狀腺功能亢進的心肌病和甲狀腺功能亢進的肺動脈高壓，在當今的醫學文獻中只有偶爾個別的病例報道。它們的自然病程，臨床進展和結果在很大程度上還不得而知。另一方面，越來越多的證據表明甲狀腺功能亢進本身，就是引起這類心臟病的唯一而直接的致病因素。在這篇綜述中，我們簡要地討論三種甲狀腺功能亢進的心臟疾病，也就是房顫、充血性心力衰竭和肺動脈高壓。

關鍵詞：房顫　心力衰竭　甲狀腺功能亢進

Introduction

Thyrotoxicosis is a common medical condition with prevalence of 2 percents in female and 0.2-0.3 percent in male.[1] The close link between the thyroid gland and the heart was evident since the first description of thyrotoxicosis for nearly two hundred years ago.[2] Many of the clinical manifestations of thyrotoxicosis are due to the ability of thyroid hormone to alter cardiovascular hemodynamic.[3] The usual coined terms to describe the association of thyrotoxicosis and its cardiac manifestations include "thyrotoxic heart disease", "thyro-cardiac disease" and "thyro-heart disease". Despite the frequent appearances of these terms in medical literatures, there has been no consensus of its definition. For simplicity, we may define "thyrotoxic heart disease" as the association between thyrotoxicosis and its cardiovascular complications. In this review, we briefly discuss the three cardiac consequences of thyrotoxicosis, namely atrial fibrillation, congestive cardiac failure and pulmonary hypertension.

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Atrial fibrillation

Prevalence

Atrial fibrillation (AF) is the most well-known cardiovascular complication in thyrotoxic patients and its clinical importance often overshadows the most common rhythm disturbance, sinus tachycardia in this population. Atrial fibrillation occurs in 5 to 20 percent of patients with thyrotoxicosis.[4-8] On the other hands, as many as 13 percent of patients with unexplained atrial fibrillation have biochemical evidence of thyrotoxicosis.[9] In these studies, they consistently showed that the prevalence of atrial fibrillation increased with age in thyrotoxic population as in general population. Also, in one of the most frequently cited study by Sandler and Wilson published nearly half century ago, the authors observed that the prevalence of atrial fibrillation was higher among thyrotoxic men than women.[10] More recently, Shimizu et al described the prevalence of atrial fibrillation in a large cohort of 13,088 thyrotoxic patients in Ito hospital in Tokyo.[11] They showed that the annual incidence of atrial fibrillation was only 1.7%, much lower than previous studies. However, similar to previous studies, the incidence of atrial fibrillation increased with age and was higher in male thyrotoxic subjects. Unfortunately, only age and sex were analyzed in this particular study but other co-morbidities and potential confounding factors had not been adjusted.

Mechanisms

In general, for atrial fibrillation to develop, three basic components are required: 1) a specific triggers; 2) a suitable substrate; and 3) modifying factors. Haissagurere et al. have demonstrated that a single source of rapid impulses, mainly originating from the pulmonary veins,[12] is the majority source of trigger for the initiation and maintenance of AF in patients with paroxysmal AF. In thyrotoxic rat model, thyroid hormone has been shown to increase automaticity and enhance triggered activity of pulmonary vein which may increase its arrhythmogenic activity similar to that observed by Haissagurere group.[13] Besides, thyroid hormone also modifies the electrophysiological properties of the atrium: shortening the atrial action potential duration and atrial refractory period, creating substrate favor the maintenance of atrial fibrillation. In addition, modifying factors particularly autonomic tone also play contributory role in the pathogenesis of atrial fibrillation in previous studies. Both parasympathetic and sympathetic stimulation shorten the atrial refractoriness which is associated with induction and maintenance of AF.

Outcomes

It is usually assumed that successful treatment of thyrotoxicosis often associates with reversion of sinus rhythm spontaneously. However, there are only a few studies in medical literatures providing information for this issue. Nakazawa et al showed that 62% thyrotoxic patients with atrial fibrillation had spontaneous sinus conversion within the first 3 to 4 months after euthyroidism, even without anti-arrhythmic agents in 1982.[14] Also, atrial fibrillation is unlikely to revert to sinus rhythm beyond this period without cardioversion. For those thyrotoxic patients with persistent atrial fibrillation after euthyroidism achieved, DC cardioversion is highly effective for sinus conversion (~90%) and sinus rhythm maintenance rates were exceedingly high (56% at tenth year) compared to non-thyrotoxic atrial fibrillation population whom underwent cardioversion.[15]

One of the most devastating consequences of atrial fibrillation is the systemic thromboembolism including stroke. However, whether thyrotoxic atrial fibrillation population is at increased risk for systemic thromboembolism has not been clearly evaluated for the time being. Two retrospective studies, both were conducted more 15 years ago, revealed a higher embolic rate in those with atrial fibrillation than those in sinus rhythm among thyrotoxic population.[16,17] However, in one of these two studies, age rather than the presence of atrial fibrillation, was the main risk factor for thromboembolism.[16] So far, there is no large prospective population study to confirm this observation.

Congestive Cardiac Failure

Although clinical heart failure can occasionally happen in the setting of thyrotoxicosis, most patients with clinical overt heart failure are simply because of persistent sinus tachycardia or atrial fibrillation, their

left ventricular systolic function is usually normal. It is understandable that for those patients with preserved left ventricular function, the clinical congestive cardiac failure may well be secondary to rapid atrial fibrillation and possibly an element of diastolic dysfunction. However, in the setting of atrial fibrillation, the contribution of left ventricular diastolic dysfunction is rather difficult to assess. It was for many years, assumed that this condition was seen only in the presence of underlying cardiovascular disease. In recent years, occasional case reports and case series were found in medical literatures, describing thyrotoxicosis as a cause of "reversible" dilated cardiomyopathy.[18-20] However, there has been an emerging concept, introduced by Levine and his coworkers, on the basis of their clinical observations of patients in whom thyrotoxicosis was the sole or principal factor leading to clinical overt heart failure and cardiomyopathy.[21,22] However, because of the "rarity" of this clinical entity, the incidences of clinical congestive cardiac failure and dilated cardiomyopathy in thyrotoxic patients are not available in current medical literatures. In addition, their nature, prognosis and reversibility remained largely unknown.

In recent years, an enlarging body of knowledge from both human and animal studies suggesting the existence of the entity of "pure thyrotoxic dilated cardiomyopathy". Substantial body of evidence indicates that an excess thyroid hormone alone can cause cardiac failure in a number of species.[23] Forfar and associates had assessed the effects of exercise on left ventricular ejection fraction measured by radio-nucleotide ventriculography in human cases with spontaneous uncomplicated hyperthyroidism.[24] They found that in hyperthyroid state, patients exhibited a high left ventricular ejection fraction at rest but paradoxically, the EF fell significant during exercise. At the same workload and heart rate during euthyroid state, patients restored a nomal rise in left ventricular ejection fraction upon exercise. These findings suggested hyperthyroid state may result in the poor cardiac reserve despite nomal resting EF.

Changes in thyroid hormone status influence cardiac action by three different routes: 1) thyroid hormone exerts a direct effect on cardiac myocytes primarily by binding to nuclear T3 receptors influencing cardiac gene expression 2) thyroid hormone increases the sensitivity of the sympathetic system in the hyperthyroid heart and 3) thyroid hormone leads to hemodynamic alterations in the periphery which results in increased cardiac filling and modification of cardiac contraction.

Most of the molecular and cellular mechanisms responsible for cardiovascular effects by thyroid hormone exert through both genomic and nongenomic effects on cardiac myocytes (Figure 1). The genomic effects of the thyroid hormone are mediated by the transcriptional activation or repression of specific target genes that encode both structural and functional proteins. Once in the cardiac myocytes, T3 enters the nucleus and interacts with specific transcriptional activators (nuclear receptor $\alpha 1$) or repressors (nuclear receptor $\alpha 2$). Occupancy of these receptors by T3, in combination with recruited cofactors, allows the thyroid hormone-receptor complex to bind (nuclear receptor $\alpha 1$) or release (nuclear receptor $\alpha 2$) specific sequences of DNA (thyroid-responsive element, TRE), that, in turn, by acting as cis- or trans-regulators, modify the rate transcription of specific target gene.[25] Figure 1 summarized transcriptional change in difference gene expression. One example is that thyroid hormone altering the gene expression in cardiac myocytes leads to changes in the proportion of myosin heavy-chain protein from beta to alpha, thereby increasing myosin V1 and decreasing myosin V3 isozyme levels which may result in relatively ineffective use of energy in ventricular myocardium.

On the other hands, hemodynamic changes secondary to peripheral vascular effect of thyroid hormone may further complicate the picture.[6,26] As a result of thyroid hormone on the heart and peripheral vasculature, there is an increase in heart rate, blood volume, left ventricular stoke volume, ejection fraction and cardiac output. Peripheral vasodilatation occurs as a result of rapid utilization of oxygen, increased metabolic end products, and induction of arterial smooth muscle cell relaxation by thyroid hormone directly. Vasodilatation results in a decrease in systemic vascular resistance by an average of 50-60%. The decrease in systemic vascular resistance plays a central role in the hyperthyroid hemodynamic changes. Vasodilatation and lack of increase in renal blood flow cause a decrease in renal perfusion pressure and an activation of the renin-angiotensin system, thus increasing sodium reabsorption

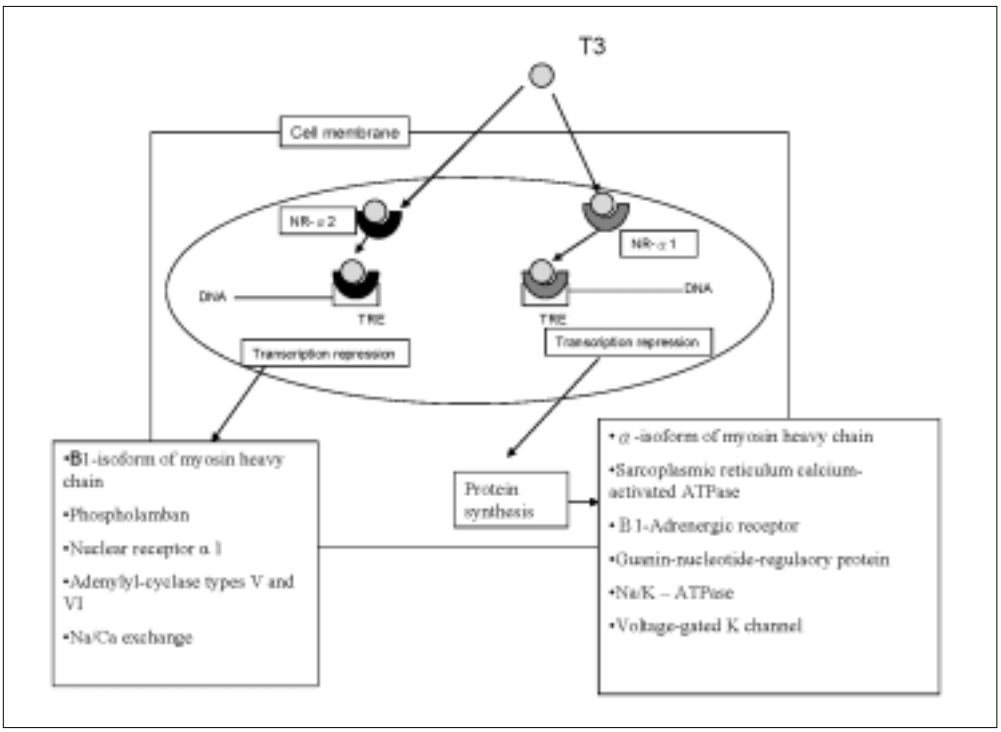

Figure 1. *Genomic effects of thyroid hormone (T3) on cardiomyocytes NR, Triiodothyronine nuclear receptor; TRE, thyroid hormone responsive element.*

and thus the blood volume. This may at the end increase the cardiac output by 2-3 folds.

It seems that in the hyperthyroid state, enormous changes in the loading situation (both pre-load and after-load) together with structural changes of the cardiac myocytes which may lead to decrease cardiac reserves, in susceptible individuals, these factors may at the end of days lead to the development of clinical overt cardiac failure in the absence of underlying heart disease.

Pulmonary Hypertension

Since early 1980s, thyrotoxicosis has been increasingly recognized as a rare cause of pulmonary hypertension as accumulating case reports and case series had been published describing this association.[27-30] In most series, pulmonary arterial hypertension were defined as the peak pulmonary systolic pressure >35 mmHg and nearly exclusively derived with echocardiographic technique. Similar to congestive cardiac failure, there has no been any large prospective population based study for this population therefore incidence, nature, prognosis and reversibility of thyrotoxic pulmonary hypertension remained largely obscure.

Two possible mechanisms have been put forwards to explain this association: 1) elevation of pulmonary vascular resistance and 2) high cardiac output in thyrotoxic state. It has been shown that there was a higher prevalence of positive anti-thyroglobulin antibody among thyrotoxic patients with isolated pulmonary hypertension (8-folds) than in the general population.[31] This observation leads to suggestion of possible autoimmune phenomenon similar to primary pulmonary hypertension, resulted in endothelial and vascular damage in thyrotoxic pulmonary hypertension. However, in the cases described by Cohen[32] and Eleftheriadis,[33] their patients presented with pulmonary hypertension and frank right heart failure, initially thought to be primary pulmonary hypertension but eventually found to be a case of thyrotoxic pulmonary hypertension. The interesting point is that in both cases, the pulmonary pressure fell back to nomal after euthyroidism achieved. This makes the possibility of autoimmune process as a cause of pulmonary vasculature damage and pulmonary

hypertension rather remote. Recently, a prospective Doppler echocardiographic study further confirmed the reversibility of pulmonary hypertension in thyrotoxicosis population.[34] In a mean follow-up time of 14±8 months, 33 thyrotoxic patients with pulmonary hypertension had significant drop in pulmonary artery systolic pressure after euthyroidism. However, it remains obscure whether the thyroid hormone exerts its effect directly on the pulmonary vasculature or the increase in cardiac output in thyrotoxic state leading to the elevation of pulmonary artery pressure, in which both may be normalized after euthyroidism.

Summary

The intimate relationship of thyroid gland and the heart can aggravate pre-existing heart disease or even lead to thyrotoxic heart diseases including atrial fibrillation, congestive cardiac failure, cardiomyopathy and pulmonary hypertension. Despite well-recognized in clinical practice, many essential clinical information including the epidemiology, outcome and management strategies, have not been fully elucidated.

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