EFFECTIVENESS OF EXERCISE TRAINING ON ASYMPTOMATIC CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES

Mr. Sompol Sanguanrungsirikul

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Health Development
Faculty of Medicine
Chulalongkorn University
Academic Year 2004

ISBN 974-53-1896-5

ประสิทธิผลของการฝึกการออกกำลังกายในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจ ที่ยังไม่แสดงอาการ

นาย สมพล สงวนรังศิริกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2547
ISBN 974-53-1896-5

Thesis Title	Effectiveness of exercise training on asymptomatic cardiac autonomic neuropathy in type 2 diabetes
By	Mr. Sompol Sanguanrungsirikul
Field of study	Health Development
Thesis Advisor	Professor Anan Srikiatkhachorn
Thesis Co-advisor	Assistance Professor Sompong Suwanvalaikorn

---

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master 's Degree

…….. Dean of the Faculty of Medicine
(Professor Pirom kamol-ratanakul, M.D., MSc.)

THESIS COMMITTEE

…….. Chairman
(Associate Professor Prasong Siriviriyakul, M.D.)

……. Thesis Advisor
(Professor Anan Srikiatkhachorn, M.D.)

…….. Thesis Co-advisor
(Assistant Professor Sompong Suwanvalaikorn, M.D.)

…….. Member
(Assistant Professor Somrat Lertmaharit, MSc., M. Med. Stat.)

สมพล สงวนรังศิริกุล: ประสิทธิผลของการฝึกการออกกำลังกายในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจที่ยังไม่แสดงอาการ. (EFFECTIVENESS OF EXERCISE TRAINING ON ASYMPTOMATIC CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES) อ. ที่ปรึกษา : ศาสตราจารย์นายแพทย์อนันต์ ศรีเกียรติขจร, อ. ที่ปรึกษาร่วม : ผู้ช่วยศาสตราจารย์นายแพทย์สมพงษ์ สุวรรณวลัยกร 62 หน้า. ISBN 974-53-1896-5

วัตถุประสงค์ของการศึกษาครั้งนี้เพื่อต้องการทราบถึงประสิทธิผลของการฝึกการออกกำลังกายในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจที่ยังไม่แสดงอาการ ได้ทำการคัดเลือกผู้ป่วยที่เต็มใจเข้าร่วมร่วมการศึกษาจำนวน 91 ราย ซึ่งเป็นผู้ป่วยที่มีการตรวจพบว่าความผิดปกติของการทำงานของระบบประสาทอัตโนมัติในระยะเริ่มแรก (ค่าคะแนนในการตรวจการทำงานของระบบประสาทออโตโนมิคของหัวใจมาตรฐาน อยู่ระหว่าง 1-2.5) แต่ยังไม่แสดงอาการทางคลินิก ทำการแบ่งกลุ่มตัวอย่างโดยวิธีสุ่ม เป็นกลุ่มควบคุม(47ราย) และกลุ่มออกกำลังกาย(44ราย) กลุ่มตัวอย่างทุกรายจะทำการตรวจวัด การทำงานของระบบประสาทออโตโนมิกของหัวใจมาตรฐาน ค่าการนำออกซิเจนเข้าสู่ร่างกายสูงสุด (VO_2peak) และ สารกลัยโคซิเลตฮีโมโกบินเอวันซี (HbA1c) ในพลาสมาก่อนและหลังการทดลอง การฝึกการออกกำลังกาย ทำโดยการใช้จักรยานวัดงาน หรือลู่วิ่ง ตลอดระยะเวลา 12 สัปดาห์ โดยความหนักของการออกกำลังกายอยู่ระหว่าง 50-60 เปอร์เซ็นต์ของความหนักสูงสุดของแต่ละบุคคล ระยะเวลาในการออกกำลังกายแต่ละครั้งอยู่ระหว่าง 30-60 นาที 3 ครั้งต่อสัปดาห์ การลดลงของคะแนนรวมในการตรวจการทำงานของระบบประสาทออโตโนมิคของหัวใจมาตรฐานเท่ากับ 1หรือมากกว่า แสดงถึงการทำงานของระบบประสาทออโตโนมิกของหัวใจดีขึ้น ผลการทดลองพบว่า กลุ่มที่ได้รับการออกกำลังกาย 12 สัปดาห์ มีผลการทำงานของระบบประสาทโอโตโนมิกที่ควบคุมการทำงานของของหัวใจดีกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ โดยกลุ่มออกกำลังกายดีขึ้น 10 ราย ในจำนวน 44 ราย(22.72%) ขณะที่กลุ่มควบคุมดีขึ้นเพียง 3 ราย จากทั้งหมด 47 ราย(6.38%), [%diff.(95%CI)=16.34%(2.13 to 30.56), P=.04] การนำออกซิเจนเข้าสู่ร่างกายสูงสุด เพิ่มขึ้นจากค่าเริ่มต้นอย่างมีนัยสำคัญทางสถิติในกลุ่มออกกำลังกาย 1.79 ± 1.51(มล./กิโลกรัม/นาที) เทียบกับกลุ่มควบคุม 0.71 ± 1.95(มล./กิโลกรัม/นาที) [mean diff.(95%CI)=1.08(0.35 to 1.82),P<.01] กลัยโคซิเลตฮีโมโกบินเอวันซี ลดลงจากค่าเริ่มต้นอย่างมีนัยสำคัญทางสถิติในกลุ่มออกกำลังกาย -0.51 ± 0.74 % เทียบกับกลุ่มควบคุม 0.06 ± 0.46% [mean diff. (95%CI)=-0.57(-0.83 to -0.32), P<.01] สรุปได้ว่า การออกกำลังกายมีผลเพิ่มการทำงานระบบประสาทออโตโนมิกของหัวใจในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจที่ยังไม่แสดงอาการ

หลักสูตร การพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา 2547 ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4575433030 : MAJOR HEALTH DEVELOPMENT PROGRAM

KEY WORD: TYPE 2 DIABETES MELLITUS / CARDIAC AUTONOMIC NEUROPATHY / EXERCISE TRAINING

SOMPOL SANGUANRUNGSIRIKUL: EFFECTIVENESS OF EXERCISE TRAINING ON ASYMPTOMATIC CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES

THESIS ADVISOR: PROFESSOR ANAN SRIKIATKHACHORN, ASST. PROF. SOMPONG SUWANVALAIKORN, 62 pp. ISBN 974-53-1896-5

The objective of this study was to evaluate the effectiveness of exercise training on asymptomatic or subclinical cardiac autonomic neuropathy in type 2 diabetes. Ninety-one patients who had been classified as mild cardiac autonomic neuropathy(standard cardiac autonomic function test score 1-2.5) were recruited. All subjects were randomly allocated into control(n=47) and exercise(n=44) groups. Subjects underwent standard cardiac autonomic function tests, measurement of peak oxygen uptake(VO_2peak), and determination of plasma glycosylated hemoglobin(HbA1c) level before and after intervention. Exercise training was performed by bicycle ergometer or treadmill for the period of twelve weeks. Exercise intensities were set at 50%-60% of individually maximum work load at VO_2 peak with duration of 30-60 minutes and frequency of 3 sessions per week. The improvement of cardiac autonomic function was defined as a decrease in autonomic cardiac function test score of $\geq$ 1. After 12 weeks of exercise training, there was significant improvement in autonomic function score of the subjects in exercise group (22.72%,n=10/44), compared with the control group(6.38%,n=3/44),[%diff.(95%CI)=16.34%(2.13 to 30.56),P=.04]. The VO_2peak was significantly increased from baseline by 1.79 ± 1.51(ml/kg/min) in the exercise group, and increased by 0.71±1.95(ml/kg/min) in the control group [mean diff.(95%CI)=1.08(0.35 to 1.82), p<.01], and the HbA1c level was significantly decreased from baseline on average by -0.51±0.74 % in the exercise group, and increased by 0.06±0.46 % in the control group [mean diff. (95%CI)= -0.57(-0.83 to -0.32), P<.01], respectively. The result of this study indicated that moderate aerobic exercise training can improve cardiac autonomic function in asymptomatic cardiac autonomic neuropathy type 2 diabetes.

Program: Health Developtment Student's signature.....

Field of study.. Health Developtment..... Advisor's signature.....

Academic year 2004 Co-advisor's signature.....

ACKNOWLEDGEMENTS

I would like to thank to my advisors, Professor Anan Srikiatkhachorn M.D. and Assistance Professor Sompong Suwanvalaikorn, M.D., for their kindness and guidance throughout the course of this study. I wish to thank to Associate Professor Prasong Siriviriyakul M.D. and Assistant Professor Somrat Lertmaharit for their suggestions in this study.

I also wish to express my special thanks to Ms. Jirapa nakanakup, Ms. Nuntawan Holaputra, and all staffs in Department of Physiology, Faculty of Medicine, Chulalongkorn University for their assistances, sincerity, and cheerfulness.

I wish to thank all volunteers for their participation in this study and express heartfelt to the Research Grant, Ratchadapiseksompotch Research Fund, Department of Research Affaires, Faculty of Medicine, Chulalongkorn University for the financial support.

Finally, my deep appreciation is extended to my lovely family for their endless support and encouragement.

CONTENTS

LIST OF FIGURES

Figure

LIST OF TABLES

Table

CHAPTER 1

INTRODUCTION

Rational and Background

Diabetes is a group of chronic metabolic disorders characterized by hyperglycaemia resulting from a relative functional deficiency in insulin through either reduced insulin secretion or reduced insulin action or both. The subsequent chronic hyperglycaemia causes glycation of tissues, which almost inevitably leads to acute disturbances in metabolism and long term end organ damage and severe health complications . Diabetes mellitus can be found in almost every population in the world and continues to increase globally . It has been estimated that between 1995 and 2025 there will be a 35% increase (from 4.0 to 5.4%) in the worldwide prevalence of diabetes and 170%increase (from 84 to 228 million) in developing countries. In Thailand, The estimated overall prevalence of diabetes in Thai adults aged >35 years was 9.6 ± 0.7%. Most of the diabetes (95.0-96.3%) in Thailand was type 2(1).

One of the common complications of diabetes is diabetic neuropathy. Diabetic neuropathy is actually a group of nerve diseases. All these disorders affect the peripheral nerves, that is, the nerves that are outside the brain and spinal cord. Some symptoms of neuropathy occur when the nerve fibers are lost. If the loss of nerve fibers affects the motor fibers, it can cause muscular weakness. If loss of nerve fibers affects the sensory fibers, it can cause loss of feeling. If it affects autonomic fibers, it can cause loss of functions not normally under conscious control.

Sensorimotor neuropathy is the most common type of neuropathy, but there is an increasing awareness of the impact of autonomic neuropathies. Diabetes autonomic neuropathy can involve the entire autonomic nervous system. Diabetes autonomic neuropathy may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal ,genitourinary, or ocular). Because of its association with a variety of adverse outcomes including

cardiovascular deaths, cardiac autonomic neuropathy is the most clinically important and well-studied form of diabetes autonomic neuropathy(2).

Perhaps one of the most overlooked of all serious complications of diabetes is cardiac autonomic neuropathy. Cardiac autonomic neuropathy results from dysfunction of the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics. The presence of cardiac autonomic neuropathy, which is usually asymptomatic, carries a considerable risk of cardiovascular mortality and morbidity compared to the general population of diabetic patients(3). In general, parasympathetic impairment precedes sympathetic dysfunction during the natural course of cardiac autonomic neuropathy in diabetic patients. Resting tachycardia due to parasympathetic damage may represent one of the earliest signs of cardiac autonomic neuropathy. Cardiac autonomic neuropathy is thought to promote the genesis of ventricular arrhythmias and silent ischemia. Striking abnormalities in the circadian pattern of autonomic nervous system activity and blood pressure regulation may trigger myocardial infarction(4). Cardiac autonomic neuropathy also produces impaired blood pressure control and can result in cardiac denervation syndrome whereby heart rate cannot be increased in response to vigorous exercise(5). In a review of several epidemiological studies among individuals diagnosed with diabetes, it was shown that the 5-year mortality rate from this serious complication is five times higher for individuals with cardiac autonomic neuropathy than for individuals without cardiovascular autonomic involvement(4, 6,7).

Long-term poor glycemic control plays a pivotal role in the pathogenic mechanism of diabetic microvascular complications including cardiac autonomic neuropathy. On the other hand, the Diabetes Control and Complications Trial (DCCT) and some other smaller prospective studies indicated that long-term near-normoglycaemia may delay or prevent the onset of abnormalities of cardiac autonomic neuropathy. A wide range of drugs has been tested but only a few have been extensively investigated in clinical trials for treating cardiac autonomic neuropathy in diabetic subjects. Previous clinical studies with aldose reductase inhibitors were negative or controversial. Recently, the use of α-lipoic acid or vitamin E proved to be promising for treating diabetic subjects with cardiac autonomic neuropathy(7,8).

Exercise has long been considered a cornerstone in the treatment regimen for patients with type 2 diabetes mellitus. Aerobic endurance exercise has traditionally been advocated as the most suitable exercise mode. Several exercise studies have evaluated the effect of exercise on insulin sensitivity and glycemic control in patients with type 2 diabetes mellitus. An evidence-based review found that the effect of aerobic or resistance training on glycemic control in type 2 diabetes is generally positive, although a dose-response relationship is indiscernible(5). Meta-analyses of structured exercise interventions in type 2 diabetes showed effectiveness of exercise for improving glycemic control by reducing HbA1c levels by 0.66%, a clinically important reduction(9). The benefits of exercise training also improved lipid profile, lower blood pressure and increased cardiovascular fitness. Exercise increases the energy expenditure, when combined with diet, can lead to bodyweight loss and decreased body fat content (10). Furthermore, systematic physical training was shown to induce improvement in the autonomic balance with a restoration to normal of the cardiovascular reflex activity in sedentary subjects (11), in hypertension, in patients with coronary artery disease and in diabetes(12,13,14,15). The controlled trial data in insulin-requiring diabetic patients was shown that aerobic exercise training improved sympathetic and parasympathetic function in subjects with subclinical or asymptomatic cardiac autonomic neuropathy but no effect in subjects with symptomatic cardiac autonomic neuropathy.(15).

In type 2 diabetes patients , there is no clinical controlled trial data in the effect of exercise training on cardiac autonomic neuropathy. The aim of the present study was to evaluate the effectiveness of exercise training on the autonomic function in diabetes patients, especially in asymptomatic cardiac autonomic neuropathy type 2 diabetes. This study was designed to investigate the potential reversibility of at least the early stages of autonomic neuropathy by those means which are available to every diabetic subject.

Research question

Does exercise training improve the cardiac autonomic reflex in type 2 diabetes patients ?

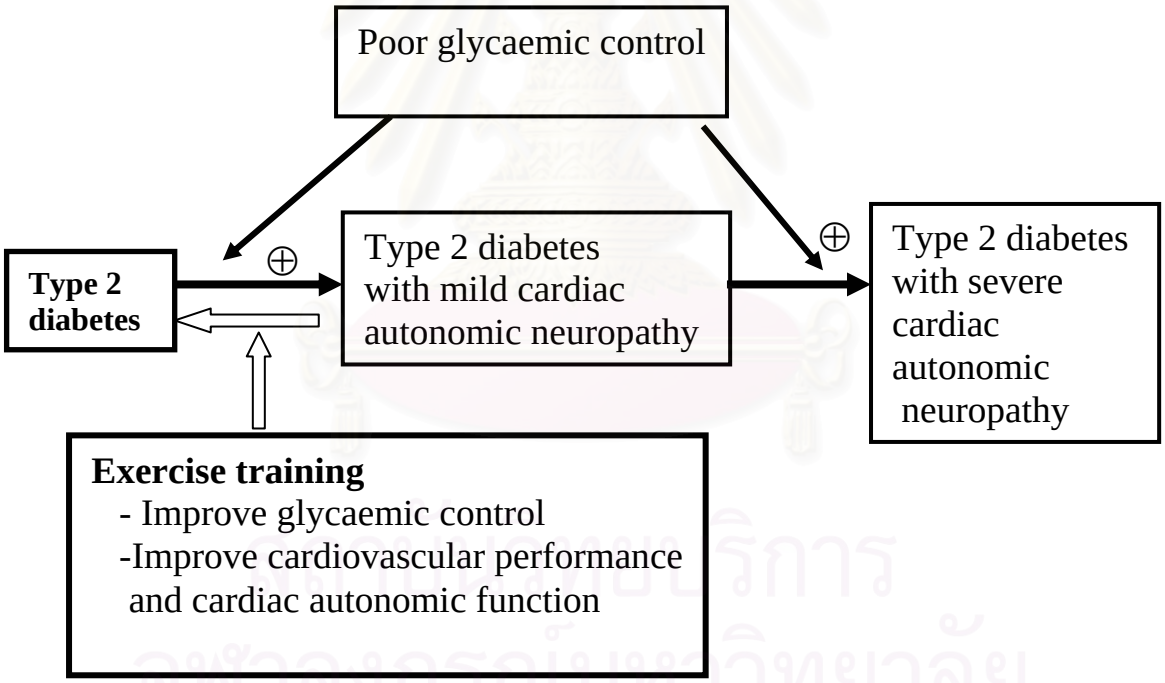
Objective

To evaluate the effect of exercise on the changes in asymptomatic cardiac autonomic neuropathy in type 2 diabetes patients.

Hypothesis

Exercise training improves the cardiac autonomic reflex in type 2 diabetes patients

Conceptual framework



Key words

Type 2 diabetes, NIDDM, cardiac autonomic neuropathy, exercise training,

Expected benefit

To know the effects of aerobic exercise training in changing cardiac autonomic function in type 2 diabetes.

CHAPTER II

REVIEW LITERATURES

Neuropathy is one of the most common complications of diabetes. When it affects the autonomic nervous system, it can damage the cardiovascular, gastrointestinal, and genitourinary systems and impair metabolic functions such as glucose counterregulation (Figure 2.1). Diabetic autonomic neuropathy impairs the ability to conduct activities of daily living, lowers quality of life, and increases the risk of death. It also accounts for a large portion of the cost of care. The autonomic nervous system is primarily efferent, transmitting impulses from the central nervous system to peripheral organs. However, it also has an afferent component. Its two divisions, the parasympathetic and the sympathetic nervous systems, work in balanced opposition to control the heart rate, the force of cardiac contraction, the dilatation and constriction of blood vessels, the contraction and relaxation of smooth muscle in the digestive and urogenital systems, the secretions of glands, and pupillary size. Diabetes can cause dysfunction of any or every part of the autonomic nervous system, leading to a wide range of disorders. And these are serious: among the most troublesome and dangerous of the conditions linked to autonomic neuropathy are known or silent myocardial infarction, cardiac arrhythmias, ulceration, gangrene, and nephropathy. Autonomic neuropathy is also associated with an increased risk of sudden death (2,3).

The autonomic nervous system and the heart (16,17)

Although automaticity is intrinsic to different cardiac tissues with pacemaker properties, the electrical and contractile activity of the myocardium is largely modulated by the autonomic nervous system. This neural regulation is effected through the interplay of the sympathetic and vagal outflows. In most physiological conditions the efferent sympathetic and parasympathetic branches have opposing actions: the sympathetic system enhances automaticity, whereas the parasympathetic system inhibits it (Figure 2.2). While the effect of vagal stimulation on the cardiac pacemaker

Diabetes can cause dysfunction of any or all parts of the automomic nervous system, leading to a wide range of disorders. (Sympathetic fibers are shown in orange, parasympathetic in blue, preganglionic solid, and postganglionic dashed.)

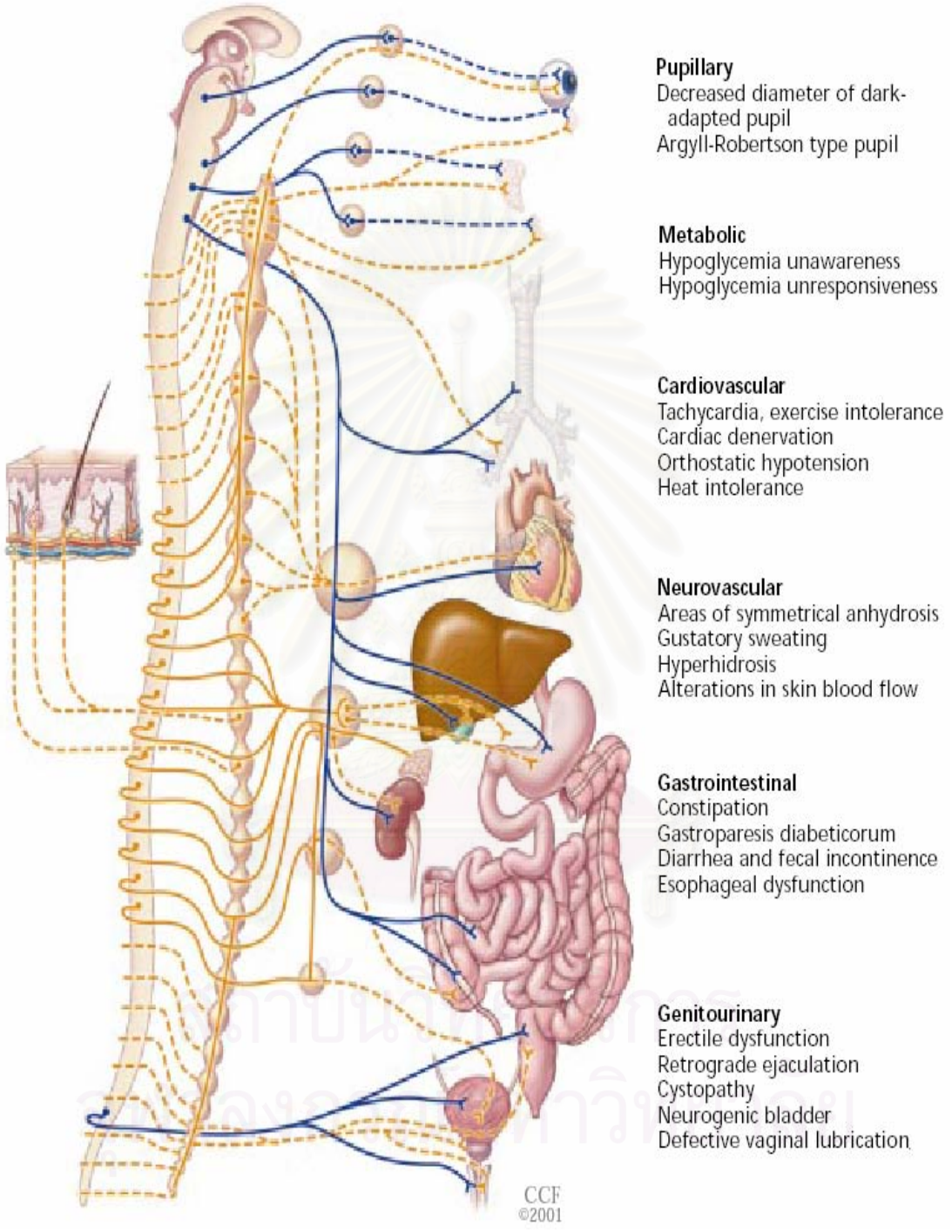


Figure 2.1. Clinical manisfestations of autonomic neuropathy (7).

cells is to cause hyperpolarization and to reduce the rate of depolarization, sympathetic stimulation causes chronotropic effects by increasing the rate of pacemaker depolarization.

Both branches of the autonomic nervous system influence ion channel activity implicated in the regulation of depolarization of the cardiac pacemaker cells . Abnormalities of the autonomic nervous system have been demonstrated in diverse conditions such as diabetic neuropathy and coronary heart disease. A dysregulation in the autonomic nervous control of the cardiovascular system associating increased sympathetic and reduced parasympathetic tone plays an important role in coronary artery disease and in the genesis of life-threatening ventricular arrhythmias. The occurrence of ischemia and/or myocardial necrosis may induce a mechanical distortion of the afferent and efferent fibers of the autonomic nervous system due to changes in the geometry related to necrotic and noncontracting segments of the heart. Newly recognized is the phenomenon of electrical remodeling due to local nerve growth and degeneration at the level of the myocardial cell in the setting of ischemia and/or myocardial necrosis. Taken as a whole, in patients with coronary artery disease and a history of myocardia infarction, cardiac autonomic function associating increased sympathetic and decreased vagal tone are conditions favourable to the complex phenomenon of life threatening arrhythmias because they modulate cardiac automaticity, conduction and importantly hemodynamic variables.

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy causes abnormalities of heart rate control and vascular dynamics. It has been linked to postural hypotension, exercise intolerance, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction. The medical consequences of cardiovascular autonomic neuropathy in diabetes are dramatic. A meta-analysis of 11 studies concluded that the 5.5-year mortality rate was 5% among patients with diabetes with normal heart-rate variability vs 27% among those with abnormal heart-rate variability(3).

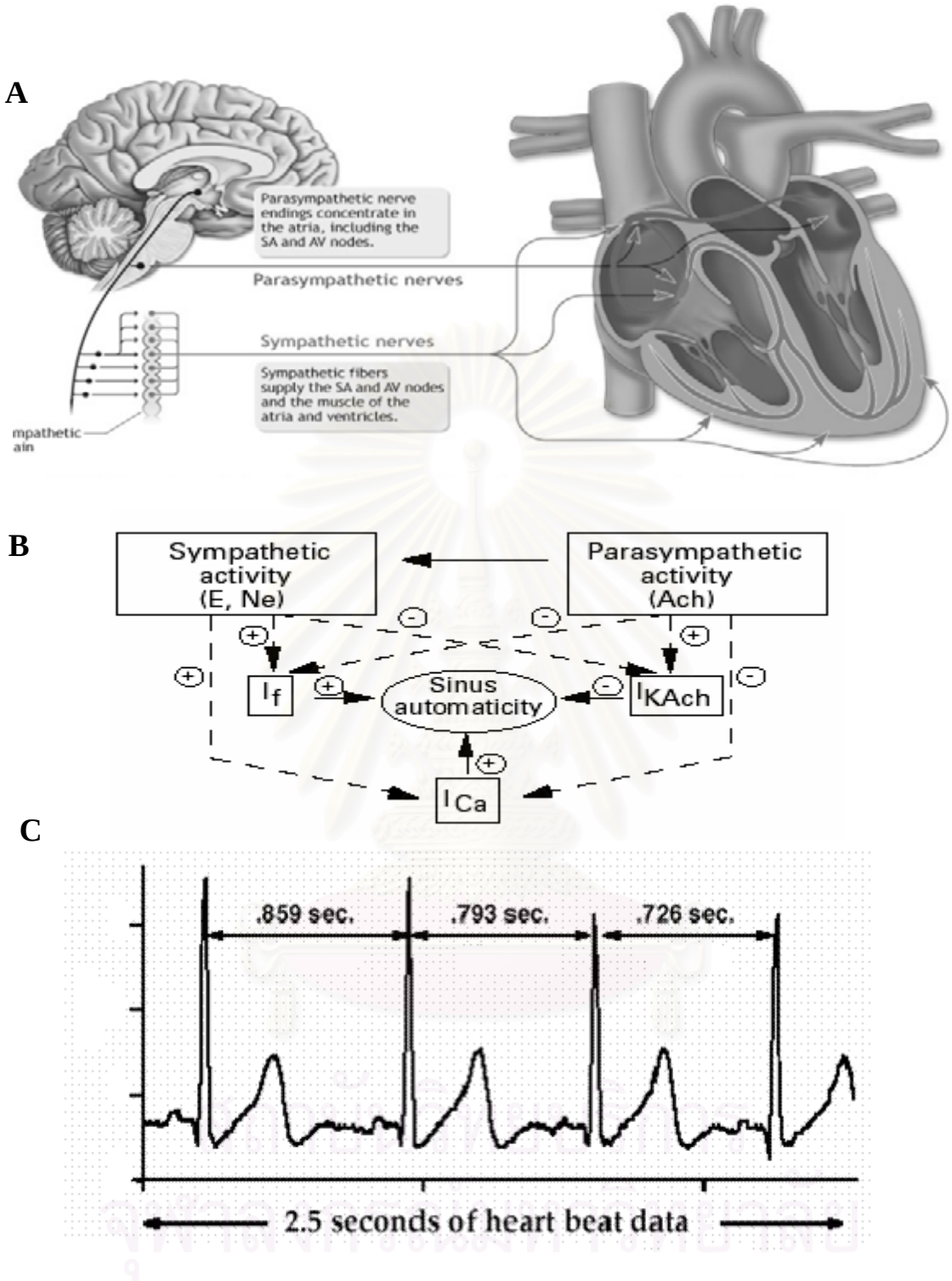


Figure 2.2 A: Pathways in autonomic control of heart rate (17),

B. The balance between sympathetic and parasympathetic activity to regulation in intrinsic heart rate (16).

C. EKG tracing showed beat-to-beat variation

Cardiac autonomic neuropathy is rapidly emerging as a key cause of morbidity and mortality in diabetes. The incidence of cardiac autonomic neuropathy appears to be around 15% in type 1 and 20% in type 2 diabetes patients. A conservative source determined the 10-year mortality rate for diabetic patients with cardiac autonomic neuropathy to be 27%, a remarkable 22 absolute percentage points higher than the mortality rate for diabetes patients without cardiac autonomic neuropathy. It is hypothesized that the comorbidity of cardiac autonomic neuropathy with coronary artery disease results in synergistic cardiovascular dysfunction, decreased myocardial infarction survival rates, and increased incidence of malignant arrhythmia and sudden death. Cardiac autonomic neuropathy affects both the sympathetic and parasympathetic innervation of the heart and coronary vessels. The hallmark symptoms are orthostatic hypotension and decreased heart rate variability, and cardiac autonomic neuropathy may contribute to left ventricular dysfunction, silent or asymptomatic myocardial infarction, and exercise intolerance. There is evidence that the disease process may begin early in the course of diabetes but remain asymptomatic until later stages (3,4).

Toyry et al have conducted a 10 years longitudinal study in patients with 138 newly diagnosed type 2 diabetes (70 men) and 144 control subjects (62 men). All subjects were examined at baseline and after 5 and 10 years of follow up. The frequency of parasympathetic neuropathy (type 2 diabetes patients versus control subjects) was 4.9 vs. 2.2% at baseline, 19.6 vs. 8.5% (P = 0.017) at 5 years, and 65.0 vs. 28.0% (P < 0.001) at 10 years of follow up(6). The frequency of sympathetic neuropathy was 6.8 vs. 5.6% at 5 years and 24.4 vs. 9.0% (P = 0.003) at 10 years of follow- up. The prevalence of combined autonomic neuropathy were 2.1 vs. 1.8% at 5 years and 15.2 vs. 4.2% (P = 0.007) at 10 years of follow up. Type 2 diabetes patients with parasympathetic neuropathy at the 10-year examination showed worse glycemic control and higher insulin values than those without parasympathetic neuropathy. Furthermore, women were more prone to have parasympathetic neuropathy than men. Parasympathetic neuropathy at baseline was more frequent in those who died from a cardiovascular cause than those who did not (13 vs. 3%, P = 0.045). Similarly,

sympathetic autonomic nervous dysfunction at the 5-year examination predicted the 10-year cardiovascular mortality (6). In the 4 years follow-up in middle-aged free coronary heart disease diabetes and nondiabetes subjects, the severity of cardiac autonomic neuropathy increased significantly form baseline in type 2 diabetes patients, but did not change in type 1 diabetes patients or control subjects. The deterioration of autonomic nervous function during the 4-years follow up was associated with poor glycemic control. Moreover, clinical manifestation of coronary heart disease was found in 7% control subjects, 37% in type 1 diabetes patients and 34% in type 2 diabetes patients at follow up examination (18).

Pathogenesis of autonomic neuropathy

Hypotheses concerning the multiple etiologies of diabetic neuropathy include a metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency. Several different factors have been implicated in this pathogenic process (Figure. 3). Hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in the NAD:NADH ratio may cause direct neuronal damage and/or decreased nerve blood flow . Activation of protein kinase C induces vasoconstriction and reduces neuronal blood flow . Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability. Alternatively, excess nitric oxide production may result in formation of peroxynitrite and damage endothelium and neurons, a process referred to as nitrosative stress . In a subpopulation of individuals with neuropathy, immune mechanisms may also be involved . Reduction in neurotrophic growth factors, deficiency of essential fatty acids , and formation of advanced glycosylation end products (localized in endoneurial blood vessels) also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function . The result of this multifactorial process may be activation of polyADP ribosylation depletion of ATP, resulting in cell necrosis and activation of genes involved in neuronal damage (19).

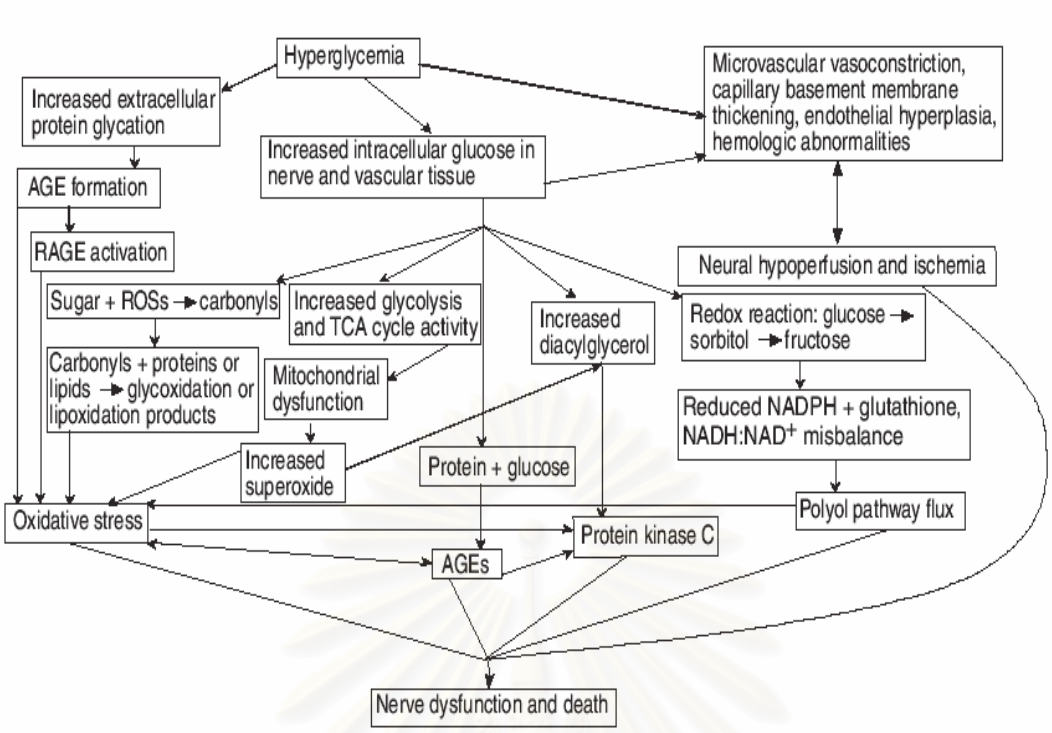


Figure 2.3. Pathogenesis of diabetes neuropathy (19)

Cardiac functional testing of the autonomic nervous system

Early detection of cardiac autonomic neuropathy is of great importance in prevention of the more advanced symptomatic stages. Undoubtedly, simple, noninvasive and reproducible tests can only be considered for testing alterations of cardiovascular innervation. From the past to present, a number of bedside cardiovascular tests are widely used. The standard battery cardiovascular reflex tests are popular due to their simplicity and reliability. There is no doubt that the diagnosis of cardiac autonomic neuropathy should be based on the results of a battery of tests rather than on a single test. Yet, rational diagnostic models were developed later in order to reduce the number of tests applied. Despite some criticisms, the standard battery cardiovascular reflex tests are still in clinical use (2,20).

Recently, measuring heart rate variability (HRV) became a popular method in characterizing autonomic dysfunction. Heart rate variability is a noninvasive electrocardiographic marker reflecting the activity of the sympathetic and vagal

components of the autonomic nervous system on the sinus node of the heart. It expresses the total amount of variations of both instantaneous heart rate and RR intervals (intervals between QRS complexes of normal sinus depolarizations) . Thus, HRV analyses the tonic baseline autonomic function. In a normal heart with an integer autonomic nervous system, there will be continuous physiological variations of the sinus cycles reflecting a balanced sympthovagal state and normal HRV . In a damaged heart which suffered from myocardial necrosis, the changes in activity in the afferent and efferent fibers of the autonomic nervous system and in the local neural regulation will contribute to the resulting sympathovagal imbalance reflected by a diminished HRV (16,20).

Prolong QT interval in EKG measurement is another diagnostic tool in assessment in autonomic impairments. Prolonged QT intervals corrected for heart rate (QTc) have been found in diabetic patients with autonomic neuropathy. A prolonged QTc is an indicator of increased risk for sudden death. Lengthening of QT/QTc intervals over time is associated with deterioration of autonomic function. Some investigators have suggested that the electrocardiographic evaluation of QT/QTc interval should be conducted to evaluate autonomic neuropathy in that this evaluation may provide some information about the risk of sudden death. It should be noted, however, that inter-observer variability with regard to the measurement of QT interval and QT dispersion is high. Thus, although this noninvasive method for identifying patients who may be at an increased risk of cardiac autonomic neuropathy is promising, one should be aware of difficulties with regard to the interpretation of QT measurements (21).

Isotope mapping (MIBG scintigraphy) of heart muscle innervation has recently been used to characterise cardiac sympathetic innervation in diabetic subjects with cardiac autonomic function test. Although the method is attractive, it is used for research purposes only (2,7).

In the present, power spectral analysis of heart-rate variations (HRV) is thought to be superior in that it detects cardiac autonomic neuropathy earlier and with greater

reliability. However, this test requires expensive additional medical equipment. It may be also more sensitive to confounders such as medication, patient age or the severity of the underlying cardiovascular disease. The standard battery of cardiovascular reflex tests might be less influenced by the mention above confounders because they are combined with a stimulus increasing either the activity of the parasympathetic nervous system or the sympathetic nervous system. Moreover, HRV did not detect cardiac autonomic neuropathy in older diabetes patients (55±10 years) better than the standard autonomic testing (**20,21,22,23**).

.Interestingly, The standard battery of cardiovascular reflex tests have been used mainly in diabetology while, on the contrary, measuring heart rate variability and assessing baroreflex sensitivity became popular predominantly in cardiology.

The standard battery of cardiovascular reflex tests .(table 2.1)

Ewing et al. proposed five simple noninvasive cardiovascular reflex tests (i.e., Valsalva maneuver, heart rate response to deep breathing, heart rate response to standing up, blood pressure response to standing up, and blood pressure response to sustained handgrip) that have been applied successfully by many investigators. The clinical literature has consistently identified these five tests as they have been widely used in a variety of studies (**2,15**).

1. Heart rate response to deep breathing (i.e., beat-to-beat heart rate variation, R-R variation). Beat-to-beat variation in heart rate with respiration depends on parasympathetic innervation. Pharmacological blockade of the vagus nerve with atropine all but abolishes respiratory sinus arrhythmia, whereas sympathetic blockade with the use or pretreatment of propranolol has only a slight effect on it . Several different techniques have been described in clinical literature, but measurement during paced deep breathing is considered the most reliable. The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while a heart monitor records the difference between the

maximum and minimum heart rates. The longest and shortest RR intervals during each breathing cycle were selected heart rate difference was calculated from the mean maximum and minimum heart rate. A difference of <=10 beats was regard as abnormal(score=1), a difference of 11-14 beats as borderline (score=0.5) and a different of >14 beats as normal(score=0).

2. Valsalva maneuver. In healthy subjects, the reflex response to the Valsalva maneuver includes tachycardia and peripheral vasoconstriction during strain, followed by an overshoot in blood pressure and bradycardia after release of strain. The response is mediated through alternating activation of parasympathetic and sympathetic nerve fibers. Pharmacological blockade studies using atropine, phentolamine (an α-adrenergic antagonist), and propranolol (a nonspecific ß-adrenergic blocker) confirm dual involvement of autonomic nerve branches for the response to this maneuver by demonstrating the drugs' varied effects of attenuation or augmentation of the hemodynamic response to the maneuver at specific times during the response . In patients with autonomic damage from diabetes, the reflex pathways are damaged. This is seen as a blunted heart rate response and sometimes as a lower-than-normal decline in blood pressure during strain, followed by a slow recovery after release. In the standard valsalva maneuver, the supine patient, connected to an EKG monitor, forcibly exhales for 15 s against a fixed resistance (40 mmHg) with an open glottis. A sudden transient increase in intrathoracic and intra-abdominal pressures, with a consequent hemodynamic response, results. With performance of the valsalva maneuver, there is a transient increase in intraocular and intracranial pressure, creating a small theoretical risk of intraocular hemorrhage and lens dislocation. In practical terms, however, the risk is minimal because comparable pressures occur in the performance of daily activities.

The valsalva ratio is determined from the EKG tracings by calculating the ratio of the longest R-R interval after the maneuver (reflecting the bradycardic response to blood pressure overshoot) to the shortest R-R interval during or shortly after the maneuver (reflecting tachycardia as a result of strain). Valsalva ratio of <=1.10 was defined as abnormal(score=1), a ratio of 1.10-1.20 as borderline(score =0.5) and a ratio of >1.2 as normal (score=0).

3. Heart rate response to standing. This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. The typical heart rate response to standing is largely attenuated by a parasympathetic blockade achieved with atropine . In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30th beat after standing. In patients with diabetes and autonomic neuropathy, there is only a gradual increase in heart rate. The patient is connected to an EKG monitor while lying down and then stands to a full upright position. EKG tracings are used to determine the 30:15 ratio, calculated as the ratio of the longest R-R interval (found at about beat 30) to the shortest R-R interval (found at about beat 15). The shortest RR interval (usually 15^{th} ± 5 beat from tilting) and after that the longest RR interval (usually 30^{th}± 5 beat) were selected and the 30/15 ratio was calculated. An abnormal 30/15 ratio was defined as $\leq$ 1.0(score=1), a ratio of 1.01-1.04 as borderline (score=0.5) and. a ratio of >1.04 as normal (score=0).

4. Systolic blood pressure response to standing. Blood pressure normally changes only slightly on standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex-mediated peripheral vasoconstriction and tachycardia. In normal individuals, the systolic blood pressure falls by <10 mmHg in 30 s. In diabetic patients with autonomic neuropathy, baroreflex compensation is impaired. A decrease in systolic blood pressure of $\geq$ 30 mmHg was regarded as abnormal (score=1), a decrease of 11-29 mmHg as borderline(score=.05) and a decrease of <10 mmHg as normal(score=0)

5. Diastolic blood pressure response to sustained handgrip. In this test, sustained muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. This rise is caused by a reflex arc

from the exercising muscle to central command and back along efferent fibers. The efferent fibers innervate the heart and muscle, resulting in increased cardiac output, blood pressure, and heart rate. The dynamometer is first squeezed to isometric maximum, then held at 30% maximum for 5 min. The normal response is a rise of diastolic blood pressure >15 mmHg. An increasing in diastolic blood pressure of ≤ 10 mmHg was defined as abnormal(score=1), an increasing of 11-15 as borderline (score=0.5) and an increasing of >15 as normal(score=1).

The sum of these was used as cardiac autonomic function score. Subject with a cardiac autonomic function score of 0–0.5 was considered as those without cardiac autonomic neuropathy, subject with score of 1–2.5 as with early/mild cardiac autonomic neuropathy and those with a score of 3–5 as subject with definite/severe cardiac autonomic neuropathy.

Table. 2.1 The standard battery of cardiovascular reflex tests

Method	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function			
1. Heart rate(R-R interval) variation during deep breathing(max.-min. heart rate)	≥15	11-14	≤10
2. Heart rate response to Valsava manoeuvre (Valsalva ratio)	≥1.21	1.11-1.20	≤1.10
3. Immediate heart rate response to standing (30:15 ratio)	≥1.04	1.01-1.03	≤1.00
Tests reflecting sympathetic function			
1. Blood pressure response to standing (fall in systolic blood pressure)	≤10 mmHg	11-29 mmHg	≥30 mmHg
2. Blood pressure response to sustained handgrip(increase in diastolic blood pressure)	≥16 mmHg	11-15 mmHg	≤10 mmHg
Score	0	0.5	1

The clinical features of autonomic neuropathy are often easily missed since they can be mild and nonspecific. Subclinical abnormalities may be present at diagnosis., This emphasizes the importance of careful screening and appropriate testing for the presence of autonomic neuropathy. Tests that evaluate the cardiovascular reflexes are most often used because of their noninvasive nature and the importance of identifying the potentially serious cardiovascular problems resulting from autonomic neuropathy.

Treatments of cardiac autonomic neuropathy (2,3,7)

Intensive glycemic control. Long-term poor glycemic control plays a pivotal role in the pathogenic mechanism of diabetic microvascular complications including cardiac autonomic neuropathy. Therefore, achieving and maintaining near-normoglycemia is essential. Interestingly, early intervention studies with intensive conservative insulin treatment, continuous subcutaneous insulin infusion or pancreatic transplantation resulted in inconsistent conclusions for clinical improvement of cardiac autonomic neuropathy On the other hand, DCCT and some other smaller prospective studies indicated that long-term near-normoglycemia may delay or prevent the onset of abnormalities of cardiac autonomic neuropathy. It can be assumed, therefore, that the advanced stages of cardiac autonomic neuropathy are more resistant to antihyperglycemic treatment than are the early stages.

Aldose reductase inhibitors and Alpha-lipoic acid. A wide range of drugs has been tested but only a few have been extensively investigated in clinical trials for treating CAN in diabetic subjects. Previous clinical studies with aldose reductase inhibitors were negative or controversial. Recently, the use of alpha-lipoic acid proved to be promising for treating diabetic subjects with cardiac autonomic neuropathy (16).

In particular, postural hypotension often needs symptomatic treatment. In clinical practice fludrocortisone proved to be most effective. The utility of other drugs (e.g. pindolol, midodrine, diltiazem, octreoide, indomethacin, erythropoietin) remains

questionable. In some cases, non-pharmacological therapy (e.g. elevation of headrest of the bed, use of elastic stockings) and avoiding hypotensive drugs (diuretics, vasodilators, etc.) are useful.

Effects of exercise interventions on glycemic control in type 2 diabetes

Most clinical trials on the effects of physical activity interventions in type 2 diabetes have had small sample sizes and therefore inadequate statistical power to determine the effects of exercise on glycemic control and body weight. Boule´ et al. (**9**) undertook a systematic review and meta-analysis on the effects of structured exercise interventions in clinical trials of duration 8 weeks on HbA1c and body mass in people with type 2 diabetes. Twelve aerobic training studies and two resistance training studies were included (totaling 504 subjects), and the results were pooled using standard meta-analytic statistical methods. The exercise and control groups did not differ at baseline in HbA1c or body weight. Postintervention HbA1c was significantly lower in exercise than control groups (7.65 vs. 8.31%, weighted mean difference 0.66%; P <0.001). In contrast, postintervention body weight did not differ between exercise and control groups. Meta-regression confirmed that the beneficial effect of exercise on HbA1c was independent of any effect on body weight. Therefore, structured exercise programs had a statistically and clinically significant beneficial effect on glycemic control, and this effect was not mediated primarily by weight loss. Although the significant effect of exercise on HbA1c in these studies is encouraging, the lack of overall effect of exercise on body weight in these studies is disappointing but not surprising. The exercise volumes and program durations (mean 53 min/session, mean 3.4 sessions/week, mean duration 15 weeks) may have been insufficient to achieve the energy deficit necessary for major weight loss. Most of these studies did not examine body composition, and loss of fat might have been partially offset by increased lean body mass.

Boule´ et al. (**24**) later undertook a meta-analysis of the interrelationships among exercise intensity, exercise volume, change in cardiorespiratory fitness, and change in HbA1c. This analysis was restricted to aerobic exercise studies in which VO_2max was

either directly measured or estimated from a maximal exercise test using a validated equation. Exercise intensities during training ranged from_50% of VO_2max to 75% of VO_2max, exercise volume 8.75–24.75 MET-hours/week. Meta-analysis revealed a clinically significant 11.8% increase in VO_2max in exercising groups, compared with a 1% decrease in control groups. Exercise intensity predicted postintervention weighted mean difference in HbA1c (r =-0.91, P = 0.002) to a larger extent than exercise volume (r = -0.46, P = 0.26).

Consistent with the above, the greatest effect of exercise on HbA1c (mean absolute postintervention HbA1c difference of 1.5% between exercise and control groups) was seen in the single study with the highest exercise intensity (25). In this study, subjects exercised at 75% of VO_2max, with intervals at even higher intensity, for 55 min three times a week, including 5 min of warm-up and 5 min of cool down. VO_2max increased 41% in the exercising subjects versus 1% in control subjects. Abdominal visceral fat assessed by magnetic resonance imaging was reported to decline by 48% and abdominal subcutaneous fat by 18% in the exercising group in this study, which are much larger fat losses than seen in most exercise studies and surprising in light of the relatively moderate total energy expenditure on exercise. This meta-analysis provides support for higher-intensity aerobic exercise in people with type 2 diabetes as a means of improving HbA1c. The analysis, however, is limited by the fact that only one study featured an unequivocally high intensity exercise program at 75% of VO_2max. This intensity might be difficult to sustain or even hazardous for many previously sedentary people with type 2 diabetes. Nevertheless, there was a strong dose-response relationship between exercise intensity across studies and both cardiorespiratory fitness and HbA1c change. These results would provide support for encouraging type 2 diabetic individuals who are already exercising at moderate intensity to consider increasing the intensity of their exercise to obtain additional benefits in both aerobic fitness and glycemic control.

The U.S. Surgeon General's report recommended that most people accumulate $\geq$ 30 min of moderate intensity activity on most, ideally all, days of the week. However,

most clinical trials evaluating exercise interventions in people with type 2 diabetes have used a three times per week frequency (9), and many people find it easier to schedule fewer longer sessions rather than five or more weekly shorter sessions. The effect on insulin sensitivity of a single bout of aerobic exercise lasts 24–72 h, depending on the duration and intensity of the activity (26). Because the duration of increased insulin sensitivity is generally not >72 h, we recommend that the time between successive sessions of physical activity be no more than 72 h (i.e., there should not be more than 2 consecutive days without aerobic physical activity).

Recommendations of aerobic exercise

The amount and intensity recommended for aerobic exercise vary according to goals. To improve glycemic control, assist with weight maintenance, and reduce risk of cardiovascular disease (CVD), we recommend at least 150 min/week of moderate-intensity aerobic physical activity (40–60% of VO_2max or 50–70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (>60% of VO_2max or >70% of maximum heart rate). The physical activity should be distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity.

Performing >4 hours/week of moderate to vigorous aerobic and/or resistance exercise is associated with greater CVD risk reduction compared with lower volumes of activity . For long-term maintenance of major weight loss ($\geq$13.6 kg [30 lb]), larger volumes of exercise (7 hours/week of moderate or vigorous aerobic physical activity) may be helpful (5).

Exercise and cardiac autonomic fuction

In case of effect of exercise on cardiac autonomic function, numerous studies have examined the relationship between exercise and cardiac autonomic function. In randomized controlled trial, Nissilä, S., et al (11) studied effect of aerobic exercise on

heart rate dynamics in sedentary subjects. The results concluded that 8 weeks exercise training including 6 sessions/wk at an intensity of 70–80% of the maximum heart rate, for 30 min/session, improvement in autonomic control of the heart. Ueno, L.M. and Mortani, T.(12) showed the improvement of parasympathetic control of heart rate in healthy subjects (aged from 60-70 years) who had been long term aerobic exercise for more than 3 days per week. Uusitalo, A. L., et al (13) studied in randomized controlled trial had shown that regular exercise training improved cardiac autonomic function in the exercise group (n=59,age 53-63 years) compared to control group(n=53). Pietila M et al (14) studied the effects of a 6-month exercise training program on heart rate and blood pressure variability, baroreflex sensitivity, myocardial blood flow, in 13 patients with New York Heart Association class II-III heart failure. The results showed that exercise training improve autonomic function by increased in baroreflex sensitivity and R-R interval variability.

Similarly, Loimaala, A., et al studied in type 2 diabetes (24 men, mean age 53.6 ± 6.2 years) in which received home-based endurance training twice a week for 12 months. They concluded that exercise training improves baroreflex sensitivity in addition to increasing the exercise capacity and improving glycemic control (27). Howorka et al demonstrated that aerobic exercise training (12 weeks, 2 session /week, with 65% of maximal performance) increased heart rate variability due to improved sympathetic and parasympathetic function in subjects with asymptomatic cardiac autonomic neuropathy (mild cardiac autonomic neuropathy, n=8), whereas in subjects with symptomatic cardiac autonomic neuropathy (severe cardiac autonomic neuropathy, n=6) no effect on heart rate variability could be demonstrated after this kind of training (11).

CHAPTER III

RESEARCH METHODOLOGY

Research design

This study was a randomized unblinded controlled trial , with 12 weeks period to assess effectiveness of exercise training program to improve cardiovascular reflex in subclinical cardiac autonomic neuropathy type 2 diabetes.

Population

Target population

Type 2 diabetes patients age 45-60 years

Study population

Type 2 diabetes patients who attended The diabetes clinic at King Chulalongkorn Memorial Hospital, Bangkok Thailand

Inclusion criteria

1. Diabetic subjects of either sex, age 45-60 years with a documented history of type 2 diabetes mellitus according to WHO criteria.
2. No history, clinical signs or symptoms of myocardial infaction, angina pectoris, stroke and peripheral vascular disease.
3. Not receiving any antiarrhythmic drugs or beta blocker. and normal EKG testing
4. Abnormal cardiac autonomic function score (1-2.5) by standard cardiac autonomic function test
5. Asymptomatic autonomic neuropathy (no clinical signs of cardiac autonomic neuropathy eg. orthostatic hypotension, resting heart rate >100 beats/min,)
6. Giving written informed consent to participate in the study prior to any study procedures
7. Ability to participate in the exercise program

Exclusion criteria

1. Coexisting diseases or conditions which may effect in the exercise testing and training, for example, severe osteoarthritis, acute infections, severe proliferative diabetic retinopathy etc.
2. Unreliable participation in visits before randomization.
3. Abnormal EKG during exercise testing protocol

Sample

Sampling techniques

Non-probability sampling (purposive sampling)

Sample size determination

$$n = \frac{[z_{\alpha}\sqrt{2p(1-p)} + z_{\beta}\sqrt{p_2[(1-p_2)+p_1(1-p_1)]}]^2}{(p_2-p_1)^2}$$

$p = (p_2+p_1)/2$

z_{α} = 1.96 for α=.05 two tailed z_{β}= 0.84 for β= 0.2 (power= 80%)

p_1 = proportion of improvement on autonomic in control group =0

There are not improvement of autonomic neuropathy over a period of 2 years follow up) (**28**).

$p_{2=}$. expected proportion of improvement on autonomic function test in exercise group =.20

Howorka et al demonstrated that aerobic exercise training (12 weeks, 2 session/week, with 65% of maximal performance) increased heart rate variability due to 20% improved sympathetic and parasympathetic function in subjects with asymptomatic cardiac autonomic neuropathy(**15**).

$p = (p_2+p_1)/2$

n for each group will be **44** patients,

Intervention (Figure 3.1.)

In this study, 783 of type 2 diabete patients were selected by review of treatment, base on assumption of inclusions and exclusions criteria, in out patient medical records. The announcements of the research project were sent to the patients by mail. There were 212 of Type 2 Diabetes aged 45-60 years called back to make appointment for participation. At the time of appointment, subjects underwent a completed history and taking physical examination by physician as well as performed electrocardiogram and cardiac autonomic function test (for details see below) .

Study subjects were randomly allocated to control group and exercise group by random number table. All subjects were informed regarding the purpose of study, expected benefits, potential risks, availability and details of alternative therapy for the disease. An assurance that the quality of medical treatment were not to be affected if consent was not given. Subjects were free to withdraw at anytime for any reason, and other requirements necessary for protection of the patient's human rights. (All aspects of the research study were in keeping with the principles embodied in the Declaration of Helsinki for experiments involving human subjects). The research proposal was approved by Institutional Review Board/Ethics Committee Faculty of Medicine Chulalongkorn University.

Cardiac autonomic function tests (Table 3.1))

To test the cardiac autonomic function test , EKG was recorded by the physiograph system (Biopac System Inc., CA, USA) with data acquisitions software (Acq*Knowledge*® version 3.7.5) for calculated heart rate and beat to beat time interval (RR interval). Blood pressure was monitor by oscillometric blood pressure monitor (Spac Lab Inc., USA).

After all surface electrodes had been placed, the subject underwent a battery cardiac autonomic function test. This battery composed heart rate variation during deep breathing, the Valsalva test, heart rate response to tilting, systolic blood pressure response to tilting and diastolic blood pressure response to sustained handgrip.

1. Heart rate variation during deep breathing. The deep breathing test was performed in a previously trained subject and consisted of taking six deep breaths within 1 min in the sitting position. The longest and shortest RR intervals during each breathing cycle were selected heart rate difference was calculated from the mean maximum and minimum heart rate. A difference of <=10 beats was regard as abnormal(score=1), a difference of 11-14 beats as borderline (score=0.5) and a different of >14 beats as normal(score=0).

2. The Valsalva test.. Conducted with the patient seated, the test consisted of forcing exhalation and maintaining a pressure of 40 mmHg for15 seconds. The result was expressed as the ratio of the longest RR interval after the manoeuver (during 30s) to the shortest RR interval during the manoeuver. Valsalva ratio of <=1.10 was defined as abnormal(score=1), a ratio of 1.10-1.20 as borderline(score =0.5) and a ratio of >1.2 as normal(score=0).

3. Heart rate response to tilting. (30/15 ratio). After 5 min rest in the supine position, the subject was tilted to the upright position and remained so for 3 min. The shortest RR interval(usually 15 ± 5 beat from tilting) and after that the longest RR interval(usually 30^{th}± 5 beat) were selected and the 30/15 ratio was calculated. An abnormal 30/15 ratio was defined as $\leq$ 1.0(score=1), a ratio of 1.01-1.04 as borderline (score=0.5) and a ratio of >1.04 as normal(score=0).

4. Systolic blood pressure response to tilting. Blood pressure was determined before tilting and the end of each minute during standing. A decrease in systolic blood pressure of $\geq$ 30 mmHg was regarded as abnormal (score=1), a decrease of 11-29 mmHg as borderline(score=.05) and a decrease of <10 mmHg as normal(score=0).

Table 3.1 Tests of Cardiovascular Autonomic Function

	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function			
1. Heart rate(R-R interval) variation during deep breathing(max.-min. heart rate)	≥15	11-14	≤10
2. Heart rate response to Valsava manoeuvre (Valsalva ratio)	≥1.21	1.11-1.20	≤1.10
3. Immediate heart rate response to standing (30:15 ratio)	≥1.04	1.01-1.03	≤1.00
Tests reflecting sympathetic function			
1. Blood pressure response to standing (fall in systolic blood pressure)	≤10 mmHg	11-29 mmHg	≥30 mmHg
2. Blood pressure response to sustained handgrip(increase in diastolic blood pressure)	≥16 mmHg	11-15 mmHg	≤10 mmHg
Score	0	0.5	1

5. Diastolic blood pressure response to sustained handgrip. The subject were asked to squeeze a handgrip dynamometer three times as heard as possible to get the maximum grip. The mean of these attempt was calculated. Then the subject was asked to squeeze the dynamometer with the force of at least 30% of mean maximal value for the period of 3 minutes. An increase in diastolic blood pressure was taken as the difference between resting value and the value before releasing handgrip. An increasing in diastolic blood pressure of ≤ 10 mmHg was defined as abnormal(score=1), an increasing of 11-15 as borderline(score=0.5) and an increasing of >15 as normal(score= 0).

Cardiac autonomic function score the sum of 5 tests was used as cardiac autonomic function score.

The score value of <1 (0-0.5) was regarded as normal

The score value of 1-2.5 was regarded as mild cardiac autonomic neuropathy

The score value $\geq$ 3 was regarded as severe cardiac autonomic neuropathy

Exercise stress test and measurement of oxygen uptake

At the beginning of this study, All of the subjects performed progressive exercise stress test by real-time monitoring electrocardiogram, oxygen consumption and carbondioxide production.

Each subject performed an exercise test on an electro-magnetically controlled cycle ergometer (Lode, MedGraphics Inc.,Minesota, USA). Briefly, After an initial 3-min warm-up at work load 25 watts (W), the power output was progressively increased by 25 W(in female) or 50 W(in male) every 3 minutes to the point of volitional exhaustion. Heart rate and EKG were monitor by Q4500 exercise stress test instrument(Quinton Inc., CA, USA). Oxygen consumption (VO_2) and carbondioxide production (VCO_2) were recorded with QMC gas analyzer (Quinton Metabolic Cart, Quinton Inc., CA, USA). The test was stopped when the subject met two of the following criteria:

1) heart rate reaches 80% HRmax of the age related theoretical maximum (220-Age),
2) the ratio of $VCo_2/ VO_2 > 1.1$,and
3) the subject was unable to continue pedaling at the prescribed rate.

Oxygen consumption at the end of the test was considered as the peak oxygen consumption (VO_2 peak). Workload at VO_2 peak was considered as individually maximum workload. This variable was measured before and after 12 weeks of training to evaluate the impact of the exercise program on the cardiovascular fitness of subjects.

Assessment of HbA1c

Plasma level of HbA1c was assessed at the endocrinology laboratory Chulalongkorn Hospital. HbA1c was assessed by immunoassay method using Cobras Mira Intrega analyzer (Roche Diasgnostic, USA)

Exercise protocol

Subjects underwent a 12-week aerobic exercise physical training program. Exercise was performed three sessions/week and all sessions were under the direct supervision of an exercise physiologist. Each session consisted of exercising on treadmill or bicycle ergometer with workload corresponding to maximal workload at VO2 peak. Intensity level was prescribed and monitored on the basis of rating of perceived exertion (RPE) scale. The guidelines of exercise session were described below.

At the first two weeks

- Stretching and warm up 10 minutes
- Exercising on treadmill or bicycle ergometer for 30 minutes at a workload corresponding to 50% of maximal workload
- Cool down 10 minutes

For the next two weeks

- Stretching and warm up 10 minutes
- Exercising on treadmill or bicycle ergometer for 45 minutes at a workload corresponding to 60% of maximal workload
- Cool down 10 minutes

For the remaining eight weeks

- Stretching and warm up 10 minutes
- Exercising on treadmill or bicycle ergometer for 60 minutes at a workload corresponding to 60% of maximal workload
- Cool down 10 minutes

Outcome measurements

Primary outcome

Primary outcome was the improvement of the cardiac autonomic function score, as defined by *decreased of cardiac autonomic function score equal to 1 or more.* The decreased in this score was implied in the improvement of cardiac autonomic regulation.

-

Secondary outcome

Secondary outcome comprised of the level of HbA1c and VO_2peak. The plasma level of HbA1c is an indicator for evaluation in glycemic status of the subject. The VO_2peak is an indicator for evaluation the cardiovascular fitness of .the subject

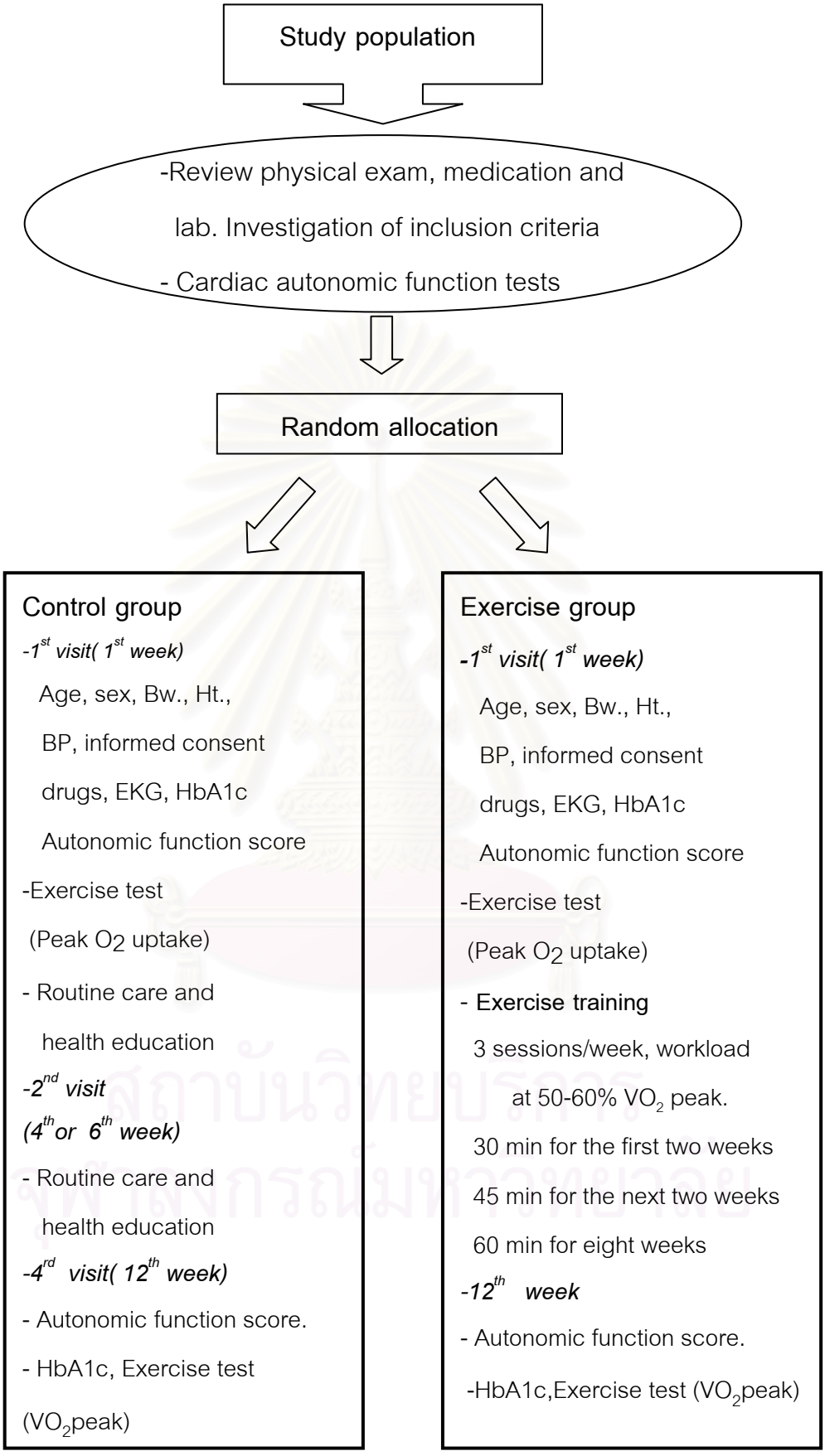


Figure 3.1 Process in intervention

Data analysis

The demographic and baseline data were presented as mean or proportions as appropriate.

1 Primary outcome

The primary outcome variable was the proportion of subjects with improvement of the autonomic function score which was defined as decrease of autonomic function score value of at least one

Statistical test

Comparisons between treatments for proportions of subjects were performed using Fisher's exact test (n of each group=44)

Hypothesis

The objective of this study was to demonstrate that the exercise training improves the cardiac autonomic reflex in type 2 diabetes patients. This study was interested in testing the following hypotheses:

H_o: $P_1=P_2$ ($P_1-P_2 = 0$).

H_A: $P_1 \neq P_2$ ($P_1-P_2 \neq 0$).

P_1 = *proportion of improvement on autonomic function test in control group*

P_2= *proportion of improvement on autonomic function test in excercise group*

2 Secondary outcome

The VO_2peak and HbA1c of each subject were secondary outcome. The level of VO_2peak and HbA1c were measured before and after 12 weeks both in control and exercise group to evaluate the exercise training effect on the cardiovascular performance and glycemic control of subjects.

Statistical test;

The test of normality was checked by histogram and Kolmogorov-Smirnov test. If data was normally distributed, unpair t-test had been employed, otherwise the Mann- Whitney test was used.

: *Hypotheses test on VO_2peak*

H_o: $\mu_1 = \mu_2$

H_A: $\mu_1 \neq \mu_2$

μ_1 = *mean difference of the VO_2 peak level of subjects in control population.*

μ_2 = *mean difference of the VO_2 peak level of subjects in exercise population.*

Hypotheses test on HbA1c

H_o: $\mu_1 = \mu_2$

H_A: $\mu_1 \neq \mu_2$

μ_1 = *mean difference of the HbA1c level of subjects in control population.*

μ_2 = *mean difference of the HbA1c level of subjects in exercise population.*

Statistical decision

All statistical tests were two-sided and performed at the overall 0.05 level of significance, reject H_o if p value <0.05

Ethical consideration

1. Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, were approved by the Chulalongkorn's Institutional Review Board/Ethics Committee.
2. The identity of the patients will be kept in confidence.
3. The patients' withdrawal from the study will not interfere with routine care or benefit

Limitation

1 Time limitation for sample collection.

2 The compliance to the exercise intervention is unexpected.

3 No dietary control in this study

4 Some of the antihypertensive drugs may be a co-intervention. In this study, oral hypoclycemic drugs, ACEI that treated microalbuminuria and lipid lowering drugs were allow to use in the study subjects. In order to decreased the effect of co-intervention, we plan to minimize the change of the drugs usages as soon as possible.

CHAPTER IV

RESULTS

Subjects were recruited continuously between October 2003 and August 2004 and the exercise program was completed by December 2004. In this study, 783 of type 2 diabete patients were selected by review of medical history and treatments in out patient medical records. The announcements of the research project had been sending to the patients by mail.

212 subjects who received the letter agreed in the study. All of them received full physical examination, review of medication, EKG and cardiac autonomic function test. Sixty five (30.1%) patients were excluded because of normal cardiac autonomic function test. Forty nine patients with cardiac function score >2.5 (n= 34), postural dizziness, resting tachycardia, hypertension or cardiac arrhythmias were subsequently excluded. Subjects were allocated using random number table to control and exercise group. There were ninety-eight patients provided informed consent. There were seven subjects in exercise group drop out after first weeks because of lack of time for training. Finally, there were ninety-one patients (male=12, female= 79) participated in this project until the end of the study. .. At the time of recruitment, none of the subjects was being treated with insulin, but each was taking an oral hypoglycemic agent: glyburide and/or metformin . Individualized dosages of oral hypoglycemic agents were unchanged throughout the study.

Demographic data

Baseline characteristics of the subjects both in control and exercise group were summarized in Table 4.1. The age of the subjects ranged form 45 to 60 year-old, with mean age of 53.6 in control group, and .54.3 in exercise group. The majorities of subject in both groups were female with body mass index approximately 26 kg/m^2.

The mean duration of diabetes in both group was around 10 years (range 4-18 yrs.). The level of HA1c(mean ± SD) of control group and exercise group was 8.34 ± 1.60 and 8.23 ±1.35 ,respectively. The peak oxygen consumption (mean ± SD) control group was 21.45 ± 2.70 ml/kg/min and 20.94 ± 1.86 ml/kg/min in exercise group. None of the subject was abnormal EKG during exercise stress test. The cardiac autonomic function score of control group and exercise group were 1.7 ± 0.6 and 1.6 ± 0.5, respectively. Results in each cardiac autonomic function test and cardiac autonomic function score were shown in Table 4.2. Interestingly, approximated 40% of subjects in both groups were abnormal in testing of heart rate variation during deep breathing.

Effect of exercise training program on cardiac autonomic function score

The improvement in cardiac autonomic function in this study was defined by decreased of cardiac autonomic function score equal to 1 or more. The decreased in this score is implying in the improvement of cardiac autonomic regulation.

In control group, all subjects (n= 47) received the information in the natural history of cardiac autonomic neuropathy and the benefits of increased physical activities including controlled diet and glycemic control. There were 21 subjects increased their physical activities (duration >20 min., 1-3 session/week) by several modality such as home based bicycle exercise, jogging, walking and Tai Chi exercise. At the 12th week of intervention, there were 3 subjects in this group improved in autonomic function score.

In exercise group, all subject (n=44) were performed exercise training program individually throughout twelfth week. Most of the subjects (39/44) preferred exercise in the evening period. There were 17 subjects performed completed exercise training program. However, none of the subject in this group performed exercise training < 2 session per week. At the end of the intervention period, there were 10 subjects in this group improved in autonomic function score.

In statistical analysis by using Fisher's exact test, there was significant improvement of the autonomic function score in exercise group compared with control group (table 4.3, $P = .04$) . Results in each cardiac autonomic function test and cardiac autonomic function score after intervention were summarized in Table 4.4.

Effect of exercise training program on HbA1c and VO_2peak

HbA1c and peak oxygen consumption for 12^{th} exercise training period were summarized in table 4.3. There was significance in plasma HbA1c level between control group and exercise group. The plasma HbA1c level decreased from baseline on average by -0.51 ± 0.74 % in the exercise group, and increased by 0.06 ± 0.46 % in the control group after the intervention (P= <.01) .

Likewise, there was significance in peak oxygen consumption among two groups. The VO_2peak (ml/kg/min) increased from baseline by 1.55 ± 1.21 in the exercise group, and increased by 0.71 ± 1.95 in the control group (P=<.01).

Table 4.1. Demographic data of the subjects

	Control group	Exercise group
Number	47	44
Age(year)	53.6 ± 5.8	54.3 ± 5.4
Gender(Male:Female)	7:40	5:39
Height (M)	1.59 ± 0.07	1.57 ± 0.06
Body weight (Kg)	65.04 ± 6.29	64.54 ± 5.69
Body Mass Index(kg/m^2)	25.69 ± 0.90	26.04 ± 1.04
Resting heart rate (beats/min)	77 ± 4	78 ± 5
Peak oxygen consumption (ml/kg of body weight/min)	18.45 ± 2.70	17.94 ± 1.86
HbA1c(%)	8.34 ± 1.60	8.23 ±1.35
Duration of diabetes (Years)	9.9 ± 4.4	10.1± 4.8
Retinopathy	6 (12.77%)	8 (18.18%)
Microalbuminuria	11(23.40%)	14 (31.82%)
Cardiac autonomic function score	1.7 ± 0.6	1.6 ± 0.5
No. subjects in score =1 (%)	14 (29.79%)	15 (34.09%)
No. subjects in score =1.5 (%)	10 (21.28%)	9 (20.45%)
No. subjects in score = 2 (%)	13 (27.65%)	14 (31.82%)
No. subjects in score = 2.5 (%)	10 (21.28%)	6 (13.64%)

Data was shown as mean ± SD

Medications included glipizide, metformin, simvastatin and enarapil

Table 4.2. The five test for cardiovascular parasympathetic and sympathetic controls in type 2 diabetes(before exercise training program).

	Control group n= 47(%)	Exercise group n=44(%)
Tests reflecting parasympathetic function		
1. Heart rate(R-R interval) variation during deep breathing		
Abnormal (score=1)	18(38.30%)	18(40.91%)
Borderline (score=0.5)	14(29.79%)	10(22.73%)
Normal (score=0)	15(31.92%)	16(36.36%)
2. Heart rate response to Valsava manoeuvre		
Abnormal (score=1)	4(8.51%)	3(6.82%)
Borderline (score=0.5)	19(40.43%)	14(31.82%)
Normal (score=0)	24(51.06%)	27(61.36%)
3. Immediate heart rate response to standing		
Abnormal (score=1)	3(6.38%)	2(4.55%)
Borderline (score=0.5)	20(42.55%)	20(45.45)
Normal (score=0)	24(51.06%)	22(50%)
Tests reflecting sympathetic function		
1. Systolic blood pressure response to standing		
Abnormal (score=1)	2(4.26%)	1(2.27%)
Borderline (score=0.5)	21(44.68%)	17(38.64%)
Normal (score=0)	24(51.06%)	26(59.09%)
2. Diastolic pressure response to sustained handgrip		
Abnormal (score=1)	5(10.64%)	4(9.09%)
Borderline (score=0.5)	24(51.06%)	26(59.09%)
Normal (score=0)	18(38.30%)	14(31.82%)

Table 4.3 Effect of exercise training on the improvement of cardiac autonomic function scores,HbA1c and peak oxygen uptake in asymptomatic autonomic neuropathy type 2 diabetes

	Control n= 47(%)	Exercise n=44(%)	Δ(95%CI)	P value
Cardiac autonomic function score				
Improve	3(6.38%)	10(22.72%)	16.34%(2.13 to 30.56)	P=.04[#]
Not improve	44(93.62%)	34(77.28%)		
HbA1c(%)				
Changes from baseline	0.06 ± 0.46	-0.51 ± 0.74	-0.57(-0.83 to -0.32)[A]	P<.01[$]
% changes	1.41 ± 5.38	-5.44 ± 6.59		
Peak oxygen consumption(ml/kgBw/min)				
Changes from base line	0.71 ± 1.95	1.79 ± 1.51	1.08(0.35 to 1.82)[A]	P=<.01*
% changes	3.58 ± 8.85	7.10 ± 5.79		

Data was shown as mean ± SD

Δ The differences were obtain by subtracting the data value of exercise group from those data of control group.

95% CI = 95% confidence interval for the net difference of change between study groups.

[A] Mean difference (95% confidence interval of the difference).

Statistical testing by Fisher's exact test.

[$] Statistical testing by Mann-Whitney test.

***** Statistical testing by student t test.

Table 4.4. Results in the five test for cardiovascular parasympathetic and sympathetic controls in type 2 diabetes after 12th week of the study.

	Control group n= 47(%)		Exercise group n=44(%)	
Tests reflecting parasympathetic function				
1. Heart rate(R-R interval) variation during				
deep breathing	Before	After	Before	After
Abnormal	18(38.30%)	16(34.04%)	18(40.91%)	5(11.36%)
Borderline	14(29.79%)	15(31.92%)	10(22.73%)	20(45.45%)
Normal	15(31.92%)	16(34.04%)	16(36.36%)	19(43.19%)
2. Heart rate response to Valsava manoeuvre				
Abnormal	4(8.51%)	4(8.51%)	3(6.82%)	2(4.55%)
Borderline	19(40.43%)	18(38.30%)	14(31.82%)	13(29.55%)
Normal	24(51.06%)	25(53.19%)	27(61.36%)	29(65.90%)
3. Immediate heart rate response to standing				
Abnormal	3(6.38%)	2(4.26%)	2(4.55%)	2(4.55%)
Borderline	20(42.55%)	21(44.68%)	20(45.45)	18(40.91%)
Normal	24(51.06%)	24(51.06%)	22(50%)	24(54.54%)
Tests reflecting sympathetic function				
1. Systolic blood pressure response to standing				
Abnormal	2(4.26%)	2(4.26%)	1(2.27%)	1(2.27%)
Borderline	21(44.68%)	22(46.81%)	17(38.64%)	16(36.36%)
Normal	24(51.06%)	23(48.93%)	26(59.09%)	27(61.37%)
2. Diastolic pressure response to sustained handgrip				
Abnormal	5(10.64%)	3(6.38%)	4(9.09%)	1(2.27%)
Borderline	24(51.06%)	25(53.19%)	26(59.09%)	25(56.82%)
Normal	18(38.30%)	19(40.43%)	14(31.82%)	18(40.91%)

CHAPTER V

DISCUSSION

The purpose in this study is to evaluate the effect of exercise on the changes in subclinical cardiac autonomic neuropathy in type 2 diabetes patients. Study population was recruited by screening based on inclusion and exclusion criteria. Although the advertisement of research projects were mail to 783 of type 2 diabetes patients, there were 212 subjects (27.1%) willing to participate in the study. The low response rate may be implied in low level of individually health care concern of type 2 diabetes patients in Thailand. 14%(7/51) drop out rate of subjects in exercise group indicated the low compliance in exercise training. In case of cardiac autonomic neuropathy, 147 patients (69.34%) were abnormal in cardiac autonomic function score. This result could not represent the prevalence of cardiac autonomic neuropathy in type2 diabetes because the sampling method was purposive in nature.

Effect of aerobic exercise training intervention on cardiac autonomic function score

Exercise training was significant improvement in autonomic function in exercise group (Table 4.3). An improvement in parasympathetic function was demonstrated in the decreased in abnormal score in the test of heart rate variation during deep breathing (Table 4.4).

Diagnosis of cardiovascular autonomic neuropathy had been using the standard battery of cardiovascular reflex test, which provided a simple and efficient staging of autonomic involvement in patients with diabetes. This scoring system uses five tests and the corresponding values commonly accepted in many studies. The following test are used: heart rate variation during deep breathing; heart rate response to valsalva maneuver; immediate heart rate response from lying to standing; fall in systolic blood pressure on standing; and increase in diastolic blood pressure during sustained

handgrip. A score from 0 to 1 is assigned to each test. If the value in one test falls in normal range a score of 0 is assigned; if it falls within the borderline range a score 0.5 is assigned, and if it fall within the abnormal range a score of 1 is assigned. The sum of the scores obtained for each test provides the final classification of the patient's degree of autonomic involvement. Thus a subject with a final score of five is classified as severely affected by autonomic neuropathy, as both the parasympathetic and sympathetic pathways may be affected.

In fact either all five tests show slight involvement, indicating dysfunction of both parasympathetic and sympathetic pathways; or three test show slight involvement and one test shows complete involvement, also indicating both parasympathetic and sympathetic dysfunction; or two test show complete involvement and one slight involvement, which likewise point to a dysfunction of both pathways. Subjects with scores of 3 to 5 are classified as severe autonomic impairment, and scores of 1 to 2.5 classified as mild autonomic impairment. Subjects scoring only 0-0.5 are classified as normal autonomic function.

In this way, the score 1 is the clinical significant in the standard battery of cardiovascular reflex test because the sum score 1 or more classified as autonomic impairment. The score 1 may be due to one test complete abnormal or two test show borderline involvement. Only one of the borderline response may be due to test mismanagement. By the basic of this scoring system, the decrease in a summation of functional score 1 or more is defined as the improvement of autonomic function in this study. On the contrary to scoring system in diagnosis, The decreased score 1 in the subjects may be due to one test reversed from abnormal to normal, or two tests reversed from borderline to normal, or two tests reversed from abnormal to borderline , respectively.

Results in the standard battery of cardiovascular reflex test in Table 4.2 indicated that the parasympathetic impairment was more prevalent than sympathetic impairment. This finding is consistent with natural history of cardiac autonomic

neuropathy which parasympathetic impairment preceded sympathetic dysfunction in diabetic patients(2,3). As shown in Table 4.3, exercise training was significantly improved in autonomic function in exercise group. An improvement in parasympathetic function was demonstrated by the decreased in abnormal score in the test of heart rate variation during deep breathing (Table 4.4.). The improvement of autonomic function in this study may be due to the beneficial of aerobic exercise in the improvement in glycemic control and cardiovascular function. The benefits of exercise training to glycemic control and cardiovascular fitness have been discussion in the next paragraph.

Beyond the effect of glycemic control and cardiovascular function, aerobic exercise training has been known to improve autonomic regulation of cardiovascular and respiratory system. Briefly, during exercise the quantity of blood pumped change in accordance with the elevated skeletal muscle oxygen demand. The cardiovascular adjustments at the beginning of exercise are rapid. Within one second after the muscle contraction there is a withdrawal of vagal (parasympathetic) outflow to the heart, which is followed by an increase in sympathetic stimulation of the heart. At the same time there is a vasodilatation of arterioles in active skeletal muscles and a reflex increase in resistance of vessels in less active area (e.g. gastro-intestinal, kidney). The end result is and increase in cardiac output to ensure that blood flow to muscle matches the metabolic needs. It is believe that cardiovascular activity can be modified by heart mechanoreceptors, muscle chemoreceptors, muscle mechanoreceptors, and baroreceptors located within the carotid arteries and the aortic arch. The fine-tuning of cardiovascular response in exercise is accomplished via a series of feedback loops from those receptors send information to the cardiovascular control center. It appears that ventilatory control during exercise has similarities to the control of the cardiovascular system. The arterial chemoreceptors and afferent neural feed back from working muscles send information respiratory control center to regulated breathing for maintain a rather constant arterial PO_2 and PCO_2. While the sympathetic activity predominates in exercising period, the parasympathetic activity is more predominant than sympathetic activity in the cessation of exercise and resting period.

Previous studies have also shown that physical fitness is related to cardiac autonomic regulation, providing evidence that aerobic training improves cardiovascular autonomic function. It has been suggested that aerobic exercise protects the heart against harmful cardiac events by increasing parasympathetic tone and also by decreasing cardiac sympathetic activity (11,27,30). Bradycardia is a well-known consequence of aerobic training and has been attributed to changes in the autonomic nervous system, i.e., either an increase in parasympathetic activity or a decrease in sympathetic activity, or else to a reduced intrinsic control of heart rate (9,11,12). The decreased abnormal test in heart rate variation during deep breathing in exercise group indicated the improvement of parasympathetic function in this study.

Effect of aerobic exercise training intervention on VO_2peak

To assess cardiovascular fitness, the most commonly accepted measurement is the peak rate of oxygen consumption (VO_2peak). VO_2peak is a function of maximal heart rate and stroke volume (amount of blood pumped per heart beat) as well as maximal peripheral oxygen extraction. VO_2peak is measured clinically to quantify functional ability and in research settings to estimate the physical activity status and fitness levels of participants. In this study, the mean VO_2peak of the subjects was (approximatedly) 18 ml/kg/min. which classified as having poor cardiovascular fitness in age-match (17). On average, patients with type 2 diabetes have VO_2peak values that are 20–25% below that reported in age- and sex-matched sedentary healthy individuals(29). Unfortunately, very few studies have ever addressed which components of VO_2peak are attenuated in type 2 diabetes (i.e. cardiac output or arterio-venous oxygen difference). However, this reduced VO_2peak in patients with type 2 diabetes may be due to impairment of left ventricular function and vascular function (29,30)..

The impairment of left ventricular function is correlates with in decrease in stroke volume, while vascular impairment correlates with blood flow distribution. Lower oxygen at peak exercise reflectes lower cardiac output at peak exercise. Lower left ventricular

end-diastolic volume index and cardiac index in diabetes patients had been related to diastolic dysfunction (as reflected by reduced left ventricular compliance). This diastolic dysfunction has been suggested to be an early manifestation of diabetic cardiomyopathy, while the systolic ventricular function is still normal. This diabetic cardiomyopathy has been postulated to be due to microvascular complication, interstitial fibrosis, autonomic dysfunction, and myocardial oxidative damage. Other possible explanations for the lower peak VO_2 in diabetic patients include impaired capillary function, thickened skeletal-muscle capillary basement membrane, and impaired nitric oxide-dependent dilation of skeletal muscle arterioles, but not activity of muscle mitochondrial enzymes, which had been found to be normal (29).

As shown in table 5, there was significantly increased in VO_2peak in exercise group, compared with the control group. The average improvement in VO_2peak in exercise training group is 7.1 %. In systematic review of 23 studies that had described the effect of aerobic-type exercise training on VO_2peak in patients with type 2 diabetes, in which the authors had documented frequency, duration , intensities and type of exercise performed. From this reviewed, the average improvement in VO_2peak associated with aerobic exercise training is 13.2% (range 0–41%) (29).. The majority of these studies had prescribed exercise three times per week for durations ranging between 40 and 60 minutes, using exercises such as walking, jogging and stationary cycling(5,10,15,29). Evidence for an exercise training benefit in cardiovascular function is strongest for improvements in endothelial vasodilator function and left ventricular diastolic function in type 2 diabetes and hypertensive patients (29,30).

Effect of aerobic exercise training intervention on HbA1c

The treatment goal in type 2 diabetic patients is to improve glycemic control. Ideally, the aim of therapy is the normalization of blood glucose levels. An additional marker of a patient's glycemic state is the level of glycosylated hemoglobin (HbA1c), which is formed by the adduction of glucose to hemoglobin. HbA1c is thought to reflect

integrated blood glucose concentration over a period of 2 months, the approximate half-life of red blood cells. Therefore, HbA1c give a more accurate indication of long-term glycemic control than random blood glucose measurements, which may be influenced by a number of factors such as the diurnal glycemic profile, and food intake of fasting prior to analysis.

In the present study, the plasma level of HbA1c was significantly reduced from baseline in exercise group (-0.51 ± 0.74,95%CI = 0.31 – 0.82). Any reduction in HbA1c is likely to reduce the risk of complications. The UK prospective diabetes study (UKPDS) studied in the association of HbA1c with macrovascular and microvascular complications of type 2 diabetes. This evidence based concluded that each 1% reduction in HbA1c was associated with reductions in risk of 21% for any end point related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular Complications (**31**).

The main effect of exercise in the improvement of glycemic control is increasing in insulin sensitivity. Aerobic exercise has a beneficial effect on insulin sensitivity in normal as well as insulin resistant populations. A distinction should be made between the acute effects of exercise and training (long term) effects. Up to two hours after exercise, glucose uptake is in part elevated due to insulin independent mechanisms, probably involving a contraction-induced increase in the amount of GLUT4 associated with the plasma membrane and T-tubules. However, a single bout of exercise can increase insulin sensitivity for at least 24 hour post exercise in healthy as well as type 2 diabetes subjects. Many studies have shown that acute exercise also enhances insulin stimulated GLUT4 translocation. Increases in muscle GLUT4 protein content contribute to this effect, and in addition it has been hypothesized that the depletion of muscle glycogen stores with exercise plays a role herein. Physical training potentiates the effect of exercise on insulin sensitivity through multiple adaptations in glucose transport and metabolism. In addition, training may elicit favorable changes in lipid metabolism and can bring about improvements in the regulation of hepatic glucose output, which is especially relevant to type 2 diabetes (**5,26**).

Conclusion

In conclusion, these findings indicate that moderate aerobic exercise training of 12 weeks duration improved cardiac autonomic function in asymptomatic cardiac autonomic neuropathy type 2 diabetes. There was improved parasympathetic function that demonstrated by decreasing abnormal function test of parasympathetic function in the standard battery of cardiovascular reflex tests. The benefits from physical training may be due to; an improvement of glycemic control, increasing in cardiovascular performance, and improvement of neural regulation during exercise and after cessation of exercise, respectively.

References

1. Aekplakorn, W., Stolk, R. P., Neal, B., Suriyawongpaisan, P. and Wooword, M. The Prevalence and Management of Diabetes in Thai Adults. Diabetes Care 26 (October 2003): 2578-2763.

2. Vinik, I. A., Maser, R. E., Mitchell, D. B. and Freeman, R. Diabetic Autonomic Neuropathy. Diabetes Care 26 (May 2003): 1553-1579.

3. . Jermendy, G. Clinical consequences of cardiovascular autonomic neuropathy in diabetic patients. Acta Diabetol 40 (April 2003): S370–S374.

4. Valensi, P., Sachs, R. N., Harfouche, B., Lormeau, B, Paries J, Cosson E, Paycha F, Leutenegger M. and Attali, J. R. Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. Diabetes Care 24 (January 2001): 339-342.

5. Sigal., J. R., Kenny, P. G., Wasserman, H. D. and Castaneda-Sceppa, C. Physical activity/exercise and type 2 diabetes. Diabetes Care 27 (October 2004): 2518-2539.

6. Toyry, J. P., Niskanen, L. K. Mantysaari, M. J., Lansimies, E. A. and Uusitupa, M. I. Occurrence predictors and clinical significance of autonomic neuropathy in NIDDM, ten-year follow-up from the diagnosis. Diabetes 45 (May 1996): 308-315.

7. Vinik, I. A. and Erbas, T. Recognizing and treating diabetic neuropathy. Cleveland and Clinic Journal of Medicine 68 (November 2001): 928-944.

8. Manzella, D., Barbieri, M., Ragno, E. and Paolisso, G. Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes. Am J Clin Nutr 73 (April 2001): 1052-1057.

9. Boule, N. G., Haddad, E., Kenny, G. P., Wells, G. A. and Sigal, R. J. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 286 (October 2001): 1218-1227.

10. American Diabetes Association. Physical activity/exercise and diabetes mellitus. Diabetes Care 26 (January 2003): S73-S77.

11. Nissilä, S., Richard, L., Heikki, V. H., Mikko, P., Tulppo, A. J., Timo, H., Raija. T. L. Effects of aerobic training on heart rate dynamics in sedentary subjects. J Appl Physiol 95 (July 2003): 364-372.

12. Ueno, M. L. and Moritani, T. Effects of long-term exercise training on cardiac autonomic nervous activities and baroreflex sensitivity. Eur J Appl Physiol 89 (February 2003): 109–114.

13. Uusitalo, A. L., Laitinen, T., Vaisanen, S. B., Lansimies, E. and Rauramaa, R. Effects of endurance training on heart rate and blood pressure variability. Clin Physiol Funct Imaging 22 (May 2002): 173-179.

14. Pietila, M., Malminiemi, K., Vesalainen, R., Jartti, T., Teras, M., Nagren, K., Lehikoinen , P. and Voipio-Pulkki, L. M. Exercise training in chronic heart failure: beneficial effects on cardiac C-hydroxyephedrine PET, autonomic nervous control, and ventricular repolarization. J Nucl Med 43 (June 2002): 773-779.

15. Howorka, K., Pumprla, J., Haber, P., Koller-Strametz, J., Mondrzyk, J.and Schabmann, A. Effects of physical training on heart rate variability in diabetic patients with various degrees of cardiovascular autonomic neuropathy. Cardiovasc Res 34 (January 1997): 206-214.

16. Sztajzel, J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly 134 (May 2004):

17. Macardle, D. W., Katch, I. F., and Katch, L. V. Essentials of exercise physiology 2nd ed. Philadelphia USA: Lippincort Williams & Wilkins. 2000: 275-295.

18. Mustonen, J., Uusitupa, M., Mantysaari, M., Lansimies, E., Pyorala, K. and Laakso, M. Change in autonomic nervous function during the 4-year follow-up in middle-aged diabetic and nondiabetic subjects initially free of coronary heart disease. J Intern Med (January 1997): 227-235.

19. Duby, J. J., Campbell, K. R., Setter, M. S., White, R. J. and Rasmussen, A. K. Diabetic neuropathy: An intensive review. Am J Health-Syst Pharm 61 (January 2004): 160-176.

20. Gerritsen, J., TenVoorde, J., Dekker, J. M., Kingma, R., Kostense, P. J., Bouter, L. M. and Heethaar, R. M. Measures of cardiovascular autonomic nervous function: agreement, reproducibility, and reference values in middle age and elderly subjects. Diabetologia 46 (March 2003): 330–338.

21. Whitsel, A. E., Boyko, J. E. and Siscovick, S. D. Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes; A meta-analysis. Diabetes Care 23 (February 2000): 241-247.

22. Tank, J., Neuke, A., Molle, A., Jordan, J. and Weck, M. Spontaneous baroreflex sensitivity and heart rate variability are not superior to classic autonomic testing in older patients with type 2 diabetes. Am J Med Sci 332 (January 2001): 24-30.

23. Aronson, D. and Burger, A. J., Diabetic autonomic neuropathy: The Clinical Interpretation of Improved. Diabetes Technology & Therapeutics 3 (January 2001): 77-79.

24. Boule, N. G., Kenny, G, P., Haddad, E., Wells, G. A. and Sigal, R. J: Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. Diabetologia 46 (May 2003): 1071–1081.

25. Mourier, A., Gautier, J. F., De Kerviler , E., Bigard, A. X., Villette, J. M., Garnier, J.P., Duvallet, A., Guezennec, C. Y. and Cathelineau, G. Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM: effects of branched-chain amino acid supplements. Diabetes Care 20 (February 1997): 385–391.

26. Wallberg-Henriksson, H., Rincon, J. and Zierath, J. R: Exercise in the management of non-insulin-dependent diabetes mellitus. Sports Med 25 (January 1998): 25–35.

27. Loimaala, A., Huikuri, V. H., Koobi, T., Rinne, M, Nenonen, A. and Vuori, I. Exercise training Improves baroreflex sensitivity in type 2 Diabetes. Diabetes 52: (July 2003): 1837–1842.

28. Karamitsos, D. T., Didangelos, T.P., Athyros, V. G. and Kontopoulos, A. G. The natural history of recently diagnosed autonomic neuropathy over a period of 2 years. Diabetes Res Clin Pract 42 (January 1998): 55-63.

29. Regensteiner, G. J. Type 2 diabetes mellitus and cardiovascular exercise performance. Rev Endocrin Met Dis 5 (February 2004): 269–276.

30. Steward, J. K. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension. JAMA 288 (October 2002): 1622-1631.

31. Stratton, M. I., Adler, I. A., Neil, W. A.H., Matthews, R. D., Manley, E. S., Cull, A. C., Hadden, D., Turner, R. C. and Holman, R. R. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321 (August 2000): 405-412.

APPENDIX I

Case record form

Title: Effectiveness of exercise training on asymptomatic cardiac autonomic neuropathy in type 2 diabetes

Principle investigator: Sompol Sanguanrungsirikul

Record ID ☐☐☐

Patient's name.....……..HN ☐☐☐☐☐☐☐☐☐☐

Baseline data

1. Age.....years
2. Sex ☐ Male ☐ Female
3. Weight.....kg. BP……..……mmHg PR……beats/min
4. Duration of disease ……..Yrs.
   - 4.1 Oral hypoglycaemic drugs
     - 4.1.1 …… dosage ……..
     - 4.1.2 ……..dosage ……
     - 4.1.3 ……..dosage ……
   - 4.2 Insulin inj. ☐ No ☐ Yes……..
5. Inclusion & exclusion criteria

	Yes	No
5.1 Type 2 diabetes	☐	☐
5.2 Age 45 – 60 years	☐	☐
5.3 Chest pain during exertion	☐	☐
5.4 Chest pain at rest	☐	☐

	Yes	No
5.5 Palpitation	☐	☐
5.6 Cardiovascular drugs	☐	☐

5.6.1 ……dosage……

5.6.2 ……dosage……

5.6.3 ……dosage……

5.7 Electrocardiogram(EKG) ☐ normal ☐ abnormal

Impression(if EKG abnormal)……

5.8 Resting heart rate >100 beats/min	☐	☐
5.9 Orthostatic hypotension	☐	☐
5.10 Impair sensory function	☐	☐

Impression (if “yes") ……

5.11 Impair proprioception	☐	☐
5.12 proliferative diabetic retinopathy	☐	☐
5.13 severe osteoarthritis	☐	☐

5.14 Another drugs

5.14.1 ……dosage……..……

5.14.2 ……dosage……

5.14.3 ……dosage……

6. **HbA1c level** *1st week*……*12th week*……..

7. **Autonomic nervous function score**

1st week

Heart rate response to Valsava manoeuvre (Valsalva ratio) score=…..

Heart rate(R-R interval) variation during deep breathing score=…..

Immediate heart rate response to standing (30:15 ratio) score=…..

Blood pressure(systolic) response to standing score=…..

Blood pressure(diastolic) response to sustained handgrip score=…..

Total score=….

12th week

Heart rate response to Valsava manoeuvre (Valsalva ratio) score=…..

Heart rate(R-R interval) variation during deep breathing score=…..

Immediate heart rate response to standing (30:15 ratio) score=…..

Blood pressure(systolic) response to standing score=…..

Blood pressure(diastolic) response to sustained handgrip score=…..

Total score=….

8. **Exercise test**

1st week

VO2 peak =……. ml/kg/min, BP at VO2 peak = ……mmHg.

Work load at VO2 peak = ……..watts

EKG at VO2 peak ☐ normal ☐ abnormal ……

12th week

VO2 peak =……. ml/kg/min, BP at VO2 peak = ……mmHg.

Work load at VO2 peak = ……..watts

EKG at VO2 peak ☐ normal ☐ abnormal ……

Notes ……

……

Program check list (exercise gr.)

lWeek	Exercise # 1		Exercise # 2		Exercise # 3		Remark
At the first two weeks (for exercise group) - Stretching and warm up 10 minutes - Exercising on treadmill or bicycle ergometer for 30 minutes at a workload corresponding to 50% of maximal workload - Cool down 10 minutes							
1	Y	N	Y	N	Y	N	
2	Y	N	Y	N	Y	N	

For week 3rd and 4th - Stretching and warm up 10 minutes - Exercising on treadmill or bicycle ergometer for 45 minutes at a workload corresponding to 60% of maximal workload - Cool down 10 minutes							
3	Y	N	Y	N	Y	N	
4	Y	N	Y	N	Y	N	
For the remaining eight weeks - Stretching and warm up 10 minutes - Exercising on treadmill or bicycle ergometer for 60 minutes at a workload corresponding to 60% of maximal workload - Cool down 10 minutes							
5	Y	N	Y	N	Y	N	
6	Y	N	Y	N	Y	N	
7	Y	N	Y	N	Y	N	
8	Y	N	Y	N	Y	N	
9	Y	N	Y	N	Y	N	
10	Y	N	Y	N	Y	N	
11	Y	N	Y	N	Y	N	
12	Y	N	Y	N	Y	N	

Y =yes(perform exercise training program), N=no

Notes ……

……

……

……

Program check list (control gr.)

lWeek	Exercise # 1		Exercise # 2		Exercise # 3		Remark (Details of physical activity)
1	Y	N	Y	N	Y	N	
2	Y	N	Y	N	Y	N	
3	Y	N	Y	N	Y	N	
4	Y	N	Y	N	Y	N	
5	Y	N	Y	N	Y	N	
6	Y	N	Y	N	Y	N	
7	Y	N	Y	N	Y	N	
8	Y	N	Y	N	Y	N	
9	Y	N	Y	N	Y	N	
10	Y	N	Y	N	Y	N	
11	Y	N	Y	N	Y	N	
12	Y	N	Y	N	Y	N	

Y =yes(perform physical activity), N=no

Notes

.....

.....

.....

.....

APPENDIX II

เอกสารชี้แจงข้อมูล/คำแนะนำแก่ผู้เข้าร่วมโครงการ

(Patient Information Sheet)

ชื่อโครงการ ประสิทธิผลของการฝึกการออกกำลังกายในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจที่ยังไม่แสดงอาการ

ชื่อผู้ทำการวิจัย น.พ. สมพล สงวนรังศิริกุล

อาจารย์ที่ปรึกษาโครงการ ศาสตราจารย์นายแพทย์อนันต์ ศรีเกียรติขจร

อาจารย์ที่ปรึกษาร่วม ผู้ช่วยศาสตราจารย์นายแพทย์สมพงษ์ สุวรรณวลัยกร

ผู้ดูแลที่ติดต่อได้

1. น.พ. สมพล สงวนรังศิริกุล ภาควิชาสรีรวิทยา คณะแพทย์ศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทรศัพท์ 02 – 256-4267 ต่อ 112, 02-241-8685

2. นางสาว จิรภา น้ำคณาคุปต์ ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทรศัพท์ 02 – 256-4267 ต่อ 127

สถานที่วิจัย

ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ความเป็นมาของโครงการ

การเกิดสภาวะที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจ เป็นผลแทรกซ้อนที่พบได้บ่อยในผู้ป่วยเบาหวาน ในกลุ่มผู้ป่วยเบาหวานชนิดที่2 พบว่ามีอุบัติการณ์ของการเกิดผลแทรกซ้อนนี้ถึง 65 เปอร์เซ็นต์ หลังจากเฝ้าติดตามผลการรักษาเป็นเวลา 10 ปี โดยสาเหตุของการ

เกิดผลแทรกซ้อนนี้ เกิดการการที่ไม่ได้มีการควบคุมระดับน้ำตาลในเลือดให้อยู่ในระดับปกติ ในผู้ป่วยเบาหวานที่มีผลแทรกซ้อนจากพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจ มักจะความเสี่ยงในการที่จะเกิดความผิดปกติ และอัตราการตายจากโรคทางระบบหัวใจ และหลอดเลือดสูงกว่ากลุ่มผู้ป่วยที่ไม่ได้มีผลแทรกซ้อนนี้[1]

ความผิดปกติจากพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจ ในผู้ป่วยเบาหวานนั้นสามารถตรวจพบโดย การทดสอบการทำงานของระบบประสาทออโตโนมิกของ Ewing ในผู้ป่วยเบาหวาน ที่มีการตรวจพบความผิดปกติจากพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจ ในระยะแรกๆนั้นผู้ป่วยจะไม่แสดงอาการของความผิดปกติของระบบประสาทออโตโนมิกออกมาให้เห็น และถ้ายังมีการควบคุมภาวะน้ำตาลในเลือดได้ไม่ดี จะเข้าสู่ภาวะที่มีอาการแสดงของความผิดปกติของระบบประสาทออโตโนมิกที่ควบคุมการทำงานของระบบหัวใจและหลอดเลือดอย่างชัดเจนอย่างชัดเจน เช่น แนวความคิดเกี่ยวกับ neuropathy ในปัจจุบันเชื่อว่าถ้าภาวะของการเสื่อมของประสาทมีการเปลี่ยนแปลงในระดับของ functional neuropathy หรือ structural neuropathy การทำงานของเส้นประสาทนั้นประสาทอาจจะกลับมาเป็นปกติได้ แต่ถ้าเส้นประสาทมีการเปลี่ยนแปลงถึงขั้นที่เรียกว่า nerve death แล้วการเสียนั้นก็จะเสียอย่างถาวร

วัตถุประสงค์

เพื่อศึกษาผลประสิทธิผลของการฝึกการออกกำลังกายในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจที่ยังไม่แสดงอาการ

รายละเอียดที่จะปฏิบัติต่อผู้เข้าร่วมโครงการ

1. ท่านจะได้รับสัมภาษณ์โดยผู้ทำการวิจัยเพื่อถามข้อมูลทั่วไป ประวัติ การบาดเจ็บในอดีต ปัจจุบัน ประวัติการรักษาที่เคยได้รับ

2. ท่านจะได้รับการขอร้องให้มาทำการทดสอบและประเมินร่างกายรวมสองครั้ง ประกอบด้วยการทดสอบความสามารถในการใช้ออกซิเจนสูงสุด การทดสอบการทำงานของระบบประสาทออโตโนมิก ตัวอย่างเลือดระหว่างการศึกษาวิจัยโดยท่านจะได้รับการเจาะเลือดระหว่างการทำการทดสอบจำนวน 2 ครั้ง ครั้งละ 3 มิลลิลิตร เพื่อตรวจวัดระดับ การควบคุมน้ำตาลในเลือด ซึ่งปริมาณเลือดนี้ไม่ทำให้ท่านเกิดภาวะโลหิตจางแต่อย่างไร รูปแบบการออกกำลังกายจะไม่หนักมาก มีเจ้าหน้าที่คอยดูแลตลอดเวลา เหนื่อยทำไม่ได้ สามารถหยุดได้โดยไม่มีข้อจำกัด ใดๆทั้งสิ้น

ประโยชน์และผลข้างเคียงที่จะเกิดแก่ผู้เข้าร่วมโครงการ

1. ท่านจะได้รับทราบถึง การทำงานของระบบประสาทออโตโนมิกของหัวใจ ผลการทดสอบสมรรถภาพการทำงานของระบบหัวใจและหลอดเลือด
2. ท่านจะมีอาการปวดเมื่อยบ้างหลังการทดสอบ โดยผู้วิจัยแนะนำหรืออธิบายการอบอุ่น ร่างกายให้กระจ่างให้ชัดเจนและอยู่ภายใต้การดูแลจากผู้ทำการวิจัยอย่างใกล้ชิด

การเก็บข้อมูลเป็นความลับ

ผู้วิจัยขอยืนยันว่า ข้อมูลเกี่ยวกับตัวท่านจะถูกเก็บไว้เป็นความลับ และจะใช้สำหรับงานวิจัยนี้เท่านั้นและชื่อของท่านจะไม่ปรากฏในแบบฟอร์มการเก็บข้อมูลและในฐานข้อมูลทั่วไป ผู้วิจัยจะใช้ฐานข้อมูลลับที่มีชื่อของท่านไว้ต่างหาก โดยมี่ผู้วิจัยเพียงท่านเดียวเท่านั้นที่ทราบรายละเอียดของข้อมูลนี้ผู้วิจัยขอกราบขอบพระคุณท่านที่ให้ความร่วมมือมาเข้าโครงการวิจัย ท่านสามารถขอถอนตัวออกจากโครงการได้ทุกเวลาและสามารถร้องเรียนเกี่ยวกับความไม่ถูกต้องในการวิจัย ได้ที่ฝ่ายวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ถนนพระราม 4 เขตประทุมวัน กรุงเทพ ฯ 10330 โดยทางคณะกรรมการพิจารณาจริยธรรมการวิจัยของคณะ ฯ พร้อมให้คำชี้แจงและความยุติธรรมแก่ท่าน หากท่านมีข้อสงสัยประการใดเกี่ยวกับ การวิจัยนี้ กรุณาติดต่อมาที่ น.พ. สมพล สงวนรังศิริกุล ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทรศัพท์ 01-759-7730

ผู้วิจัยขอยืนยันว่า ข้อมูลเกี่ยวกับตัวท่านจะถูกเก็บไว้เป็นความลับ และจะใช้สำหรับงานวิจัยนี้เท่านั้นและชื่อของท่านจะไม่ปรากฏในแบบฟอร์มการเก็บข้อมูลและในฐานข้อมูลทั่วไป ผู้วิจัยจะใช้ฐานข้อมูลลับที่มีชื่อของท่านไว้ต่างหาก โดยมี่ผู้วิจัยเพียงท่านเดียวเท่านั้นที่ทราบรายละเอียดของข้อมูลนี้ผู้วิจัยขอกราบขอบพระคุณท่านที่ให้ความร่วมมือมาเข้าโครงการวิจัย ท่านสามารถขอถอนตัวออกจากโครงการได้ทุกเวลาและสามารถร้องเรียนเกี่ยวกับความไม่ถูกต้องในการวิจัย ได้ที่ฝ่ายวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ถนนพระราม 4 เขตประทุมวัน กรุงเทพ ฯ 10330 โดยทางคณะกรรมการพิจารณาจริยธรรมการวิจัยของคณะ ฯ พร้อมให้คำชี้แจงและความยุติธรรมแก่ท่าน หากท่านมีข้อสงสัยประการใดเกี่ยวกับ การวิจัยนี้ กรุณาติดต่อมาที่ น.พ. สมพล สงวนรังศิริกุล ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทรศัพท์ 01-759-7730, 02-2564267 ต่อ 127

ใบยินยอมเข้าร่วมการวิจัย (Consent form)

การวิจัยเรื่อง ประสิทธิผลของการฝึกการออกกำลังกายในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีพยาธิสภาพของระบบประสาทออโตโนมิกของหัวใจที่ยังไม่แสดงอาการ

วันให้คำยินยอม วันที่ ..... เดือน.....พ.ศ.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่เกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้ และเข้าร่วมโครงการวิจัยนี้ โดยสมัครใจ และการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็น ด้วยเหตุผลทางวิชาการเท่านั้น

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม.....ผู้ยินยอม
(.....)

ลงนาม.....พยาน
(.....)

ลงนาม.....ผู้ทำวิจัย
(.....)

BIOGRAPHY

Dr. Sompol Sanguanrungsirikul was born in 1959. He graduated Master of Science in Physiology, Doctor of Medicine and Graduated Diploma in pediatrics from Chulalongkorn University.

He is currently an Assistance Professor and a staff of Department of Physiology Faculty of Medicine Chulalongkorn University.

He married his wife, Mrs Daow sanguanrungsirikul, and has a son