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Electrophysiology and kinesiology for health and disease

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Abstract

This paper summarizes my Basmajian keynote presentation at the 2004 International Society of Electrophysiology and Kinesiology Conference. I dedicate this paper to Dr. Herbert A. deVries, the mentor of my research career. The following topics will be covered from the standpoint of Electrophysiology and Kinesiology for health and disease: (1) electromechanical manifestations of neuromuscular fatigue and muscle soreness, (2) cardiac depolarization–repolarization characteristics of normal and patients, (3) etiology of obesity and diabetes and autonomic nervous system, and (4) functional electrical stimulation for health and disease, respectively.

1. Electromechanical manifestations of neuromuscular fatigue and muscle soreness

1.1. Delayed onset of muscle soreness

Every sports participant would experience muscle soreness after training. A typical feature of muscle soreness is its delayed onset, and therefore this type of muscle soreness is usually called delayed onset of muscle soreness (DOMS) [27]. It is the sensation of discomfort or pain in the skeletal muscles that occur following unaccustomed eccentric exercise [3]. It can usually be felt within 8 or 10 h after exercise, peaks between 24 and 48 h and it is gone in about 5–7 days post-exercise. Sore muscle can be described as being stiff or tender because there is a sense of reduced mobility or flexibility, and the muscles are sensitive, particularly upon palpation or movement, sometimes feeling swollen [47]. The most commonly raised possibly cause of DOMS are: (i) damage to the muscle fibers themselves, connective tissue, (ii) edema, inflammation and swelling, and (iii) a vicious cycle of reflex muscle activity, ischemia and pain–spasm theory. Although a number of different mechanisms were proposed in the past, the exact nature of this DOMS and its association to the spinal alpha motoneuron excitability and blood circulation has not yet clearly been established.

We investigated the physiological effects of static stretching upon DOMS in conjunction with the spinal alpha motoneuron pool excitability and peripheral muscle blood flow in seven healthy male subjects. All subjects performed heel raises (30 rep, 5 sets) with 20 kg load 24 h prior to testing. Electrophysiological measurements included the Hoffman reflex amplitude (H amplitude) as a measure of spinal alpha motoneuron pool excitability. The directly evoked muscle action potential (M-wave) remained constant for each subject throughout the experiments. The posterior tibia nerve was electrically stimulated for this purpose [38]. Blood flow was performed by near infrared spectroscopy (NRS). In the experimental condition (EXP), those measurements were obtained before/after static stretching (35 s, 3 sets) under experimentally induced muscle soreness. During the control condition (CON), the same measurements were made before/after standing rest for a period of 4 min. The order of the experimental treatments (EXP or CON) were chosen at random.

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Fig. 1 represents a typical set of H-reflex data obtained 24 h after experimentally induced muscle soreness prior to muscle stretching and immediately after muscle stretching. The data clearly indicated that H-reflex amplitude was considerably reduced after muscle stretching. Group data demonstrated that the static stretching brought about a statistically significant reduction in the H/M ratio (23.5%, $p < 0.01$) of the EXP conditions while no such changes were observed in CON trials. These changes were accompanied by nearly 78.5% increase ($p < 0.01$) in blood flow after stretching of the leg with the experimentally induced soreness. The result of reduction in alpha motoneuron excitability was entirely consistent with earlier studies, suggesting that the inverse myotatic reflex (Ib inhibition) may be the basis for the relief of muscle soreness by static stretching. The increase in blood flow after stretching found in the present study suggested that static stretching could bring about a relief of spasm, which could have caused local muscles ischemia and pain. Our data strongly suggest that static stretching plays a significant role in relief of DOMS by reducing spinal motoneuron pool excitability and enhancing muscle blood flow (see Fig. 2).

1.2. Fusimotor sensitivity after prolonged stretch shortening cycle exercise

We have recently performed comparative analyses of T-reflex, elicited by Achilles tendon tap and H-reflex, elicited by electrical stimulation of tibial nerve before and immediately after, 2- and 24-h after two hours of exhaustive running ($n = 10$). Results revealed that immediately after the running T and H wave amplitudes were significantly depressed while maximal M-wave remained constant. On the other hand, 2-h after the running H-reflex amplitudes showed clear-cut rising ($p < 0.001$) and by contrast, the T-reflex amplitude did not show such a significant elevation. All the EMG amplitudes recovered to the preexercise level in 24 h. The impact force on the Achilles tendon (coefficient of rebound force) showed a reduction immediately after the running ($p < 0.05$) and recovered in 24 h. The difference between H- and T-reflex amplitudes 2-h after the exhaustive running might suggest that the sensitivity of fusimotor activity was reduced by 2-h of running. Furthermore the reduced impact force might signify deteriorated stiffness regulation of muscle-tendon complex. This may also suggest the degradation of spindle activity. Therefore, present results support the hypothesis claiming that the stretch reflex reduction might be attributed to disfacilitation of alpha motoneuron pool caused by withdrawal of spindle-mediated fusimotor support and/or fatigue of the intrafusal fibers of muscle spindle itself [4,5].

1.3. Use of mechanomyogram for analysis of motor unit activity

Previous studies have indicated that mechanomyogram (MMG) amplitude and frequency components might represent the underlying motor unit (MU) recruitment and firing rate (rate coding) [6,49–52]. Interestingly, MMG amplitude actually decreases at higher force levels at which MUs might be firing at tetanic rates, causing a fusion-like contraction leading to diminished MMG amplitude, while its frequency increases [41,73,74]. These data suggest that MMG analyses might offer not only MU recruitment and rate coding characteristics, but also their mechanical properties, i.e., the fusion properties of activated MUs that could not be obtained by conventional EMG analyses [41,74].

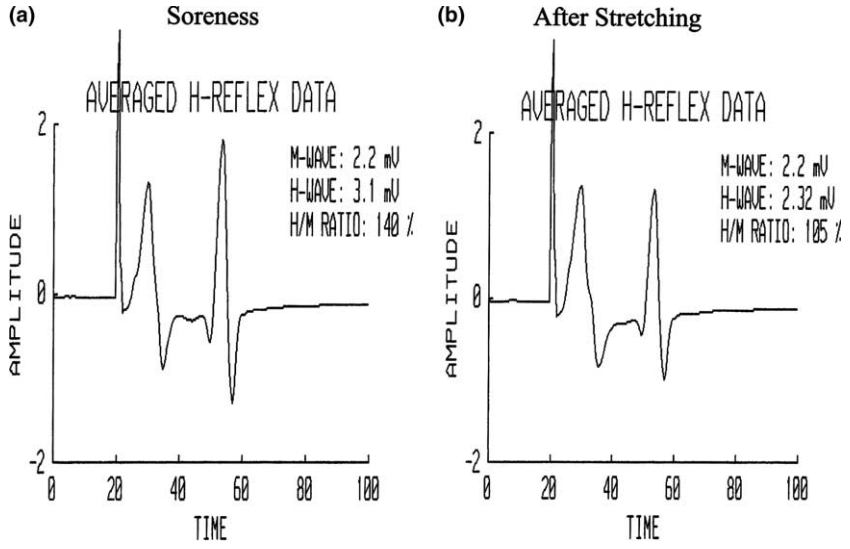

Fig. 1. Spinal motoneuron excitability (H-reflex) changes following experimentally-induced muscle soreness (a) and after static muscle stretching (b).

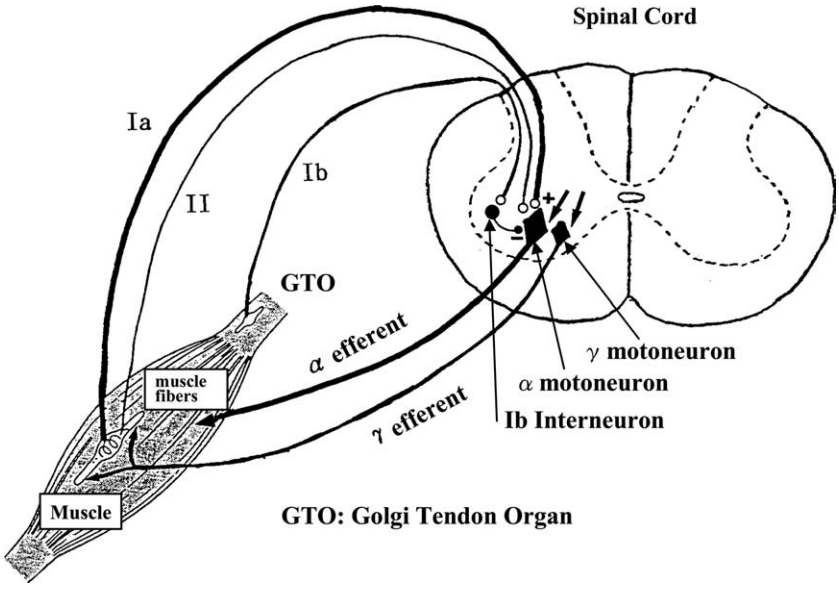

Fig. 2. A simplified schematic representation of basic neural components involved in stretch reflex and Golgi tendon organ Ib inhibition.

To further shed some light on this matter, we studied 14 isolated MUs in the medial gastrocnemius (MG) muscle of 7 healthy male subjects. Two identical microphone sensors (10 mm diameter, mass 5 g, bandwidth 3–2000 Hz) for MMG recording were fixed to the center of the belly of the MG and soleus (SOL). Single twitch and repetitive stimulations (10 Hz) were performed during room temperature and hypothermic conditions (15, 20, and 25 °C) [26]. During voluntary contractions, MU and MMG activities were recorded at 20%, 40%, 60%, and 80% MVC. Effects of mixed micro-stimulations were also studied by stimulating two MUs at 5–10, 10–20, 8–12, and 12–24 Hz, respectively; while simultaneously recorded evoked mass action potentials (M-wave) remained constant. In addition, isolated MU fatigue trials were performed at 12 Hz for a period of 2-min in order to determine the relationship between muscle contractile slowing and the corresponding MMG amplitude and frequency components (see Fig. 3).

The group data indicated that rms-MMG of MG increased as a function of force ($p < 0.01$). On the contrary, these values for SOL increased up to 60% MVC ($p < 0.01$), but then decreased at 80% MVC due to possible MU fusion resulting in smaller muscle dimensional changes [41,73]. Similarly, a significant reduction in the muscle contractile properties (peak force, maximal rate of force development and relaxation, contraction and half-relaxation times, etc.) caused by the experimental hypothermia also resulted in significant reduction in MMG amplitude with subsequent fusion at a low stimulation frequency [26]. Different stimulation frequency trials indicated that there were highly significant and progressive reductions in the force fluctuations from 5 to 50 Hz that were almost mirrored by the similar and significant reductions in the MMG amplitudes. Mixed stimulations to different MUs clearly demonstrated that both MMG and force recordings showed two distinguished peak frequencies that were delivered to the underlying MUs. Lastly, our MU fatigue study with prolonged stimulation at 12 Hz demonstrated that MMG amplitude decreased progressively as contractile slowing occurred as a function of time (see Fig. 4).

1.4. Mechanomyogram changes during low back muscle fatigue

As a practical application of this MMG analysis, we have recently investigated the etiology of low back muscle fatigue by means of simultaneous recordings of EMG, MMG, and near infrared spectroscopy (NIRS) in an attempt to shed some light on the electrophysiologic, mechanical, and metabolic characteristics, respectively [75]. Eight male subjects performed back extension isometrically at an angle 15° with reference to the horizontal plane for a period of 60s. Surface EMG, MMG and NIRS signals were recorded simultaneously from the center of the belly of L3. NIRS were measured to determine the level of muscle blood volume (BV) and oxygenation (Oxy-Hb). The root mean square amplitude value (rms) of EMG significantly increased at the initial phase of contraction and then fell significantly while mean power frequency (MPF) of EMG was significantly and progressively decreased as a function of time. There were also significant initial increases in rms-MMG, which was followed by progressive decreases at the end of fatiguing contractions. MPF-MMG remained unchanged. BV and Oxy-Hb dramatically decreased at the onset of the contraction and then

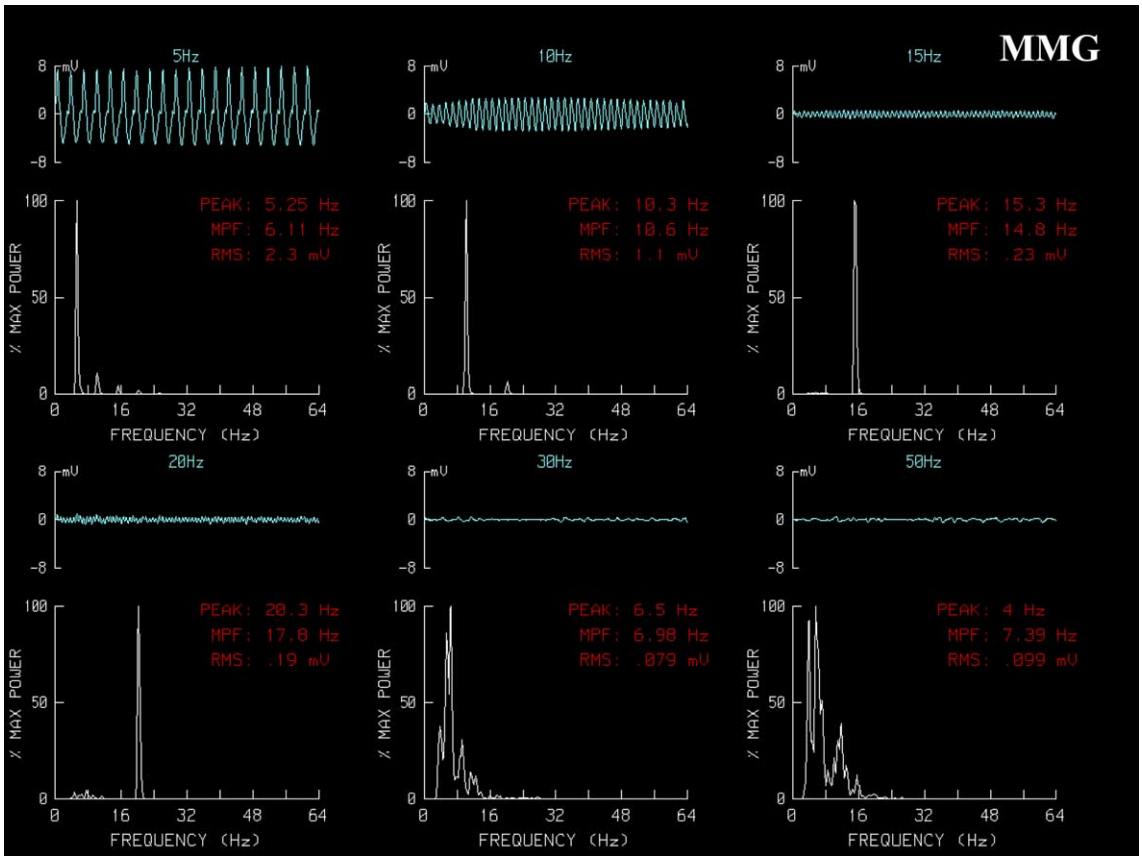

Fig. 3. Mechanomyogram changes obtained from isolated motor unit during direct stimulation at different frequencies.

remained almost constant throughout the rest of contraction. These results obtained by simultaneous recordings of EMG, MMG, and NIRS tools demonstrates that restriction of blood flow due to the high intramuscular mechanical pressure is one of the most important factors to evoke the muscle fatigue particularly in low back muscle. In addition, our simultaneous recording system described here can obtain more reliable information regarding the mechanism(s) of low back muscle fatigue.

2. Cardiac depolarization–repolarization characteristics of normal and patients with long QT syndrome (LQTS)

Cardiac autonomic dysfunction is prevalent in cardiac and diabetic patients and associated with prolongation of the myocardial repolarization period. It has been speculated that changes in autonomic nervous system activity, particularly the sympatho-vagal balance contributes to the prolongation of myocardial repolarization. Therefore, a prolonged heart rate-adjusted ECG QT duration (QTc) has been used as a marker for sudden cardiac death in myocardial infarction patients [61,62]. There is also increasing evidence that a prolonged QTc is predictive of coronary heart disease mortality in healthy populations as well [60]. Although the importance of the QTc interval is clearly recognized, it is often difficult to determine the end of the T(U) wave and to measure the QT interval precisely because of a variety of morphological T(U) wave abnormalities such as biphasic, or notched T-waves in patients [60]. In the latent or borderline patients, exercise stress testing, isoproterenol infusion, or autonomic maneuvers such as the Valsalva maneuver or the cold pressure test are reported to be helpful in unmasking a prolonged QT interval. However these provocative maneuvers are stressful and may occasionally be dangerous in some LQTS patients.

Therefore, attempts to identify new quantitative ECG characteristics of LQTS using a computer algoritlm have recently been made [7,21]. For example, the activation recovery interval (ARI), defined as the interval between the minimum dV/dt of the QRS and the maximum dV/dt in the ST–T segment on ECG, has been proposed as a useful measure of local repolarization duration. Likewise, transmembrane activation time (AT) has been reported to occur at the intrinsic deflection, the interval between ECG QRS onset to the time of maximal dV/dt of the T waves. More recent studies including our own work [67,70] have estimated the myocardial depolarization–repolarization process in terms of recovery

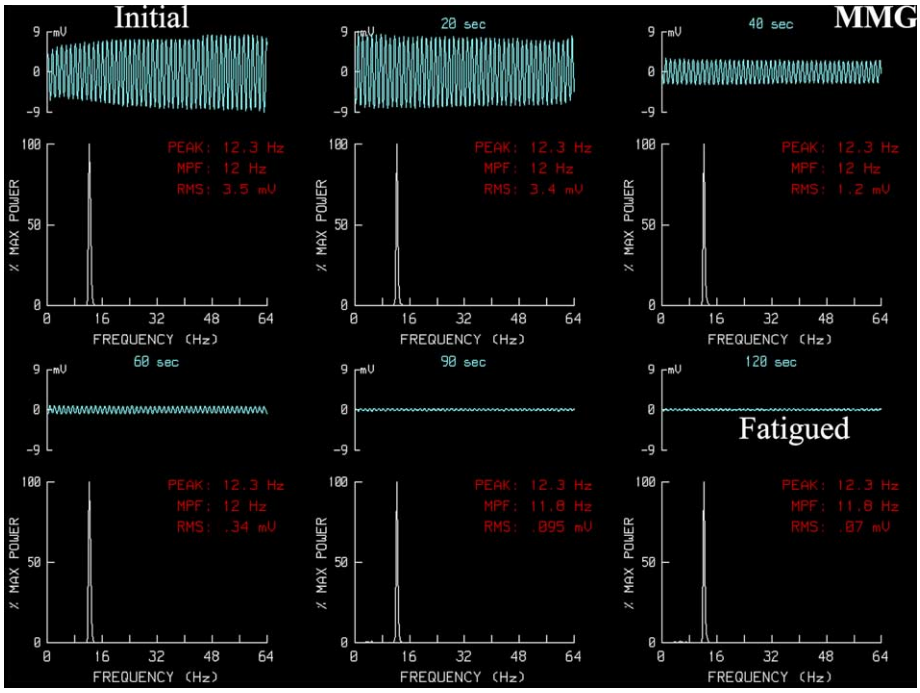

Fig. 4. Mechanomyogram changes obtained from isolated motor unit during 12 Hz prolonged fatigue stimulation.

time (RT) defined as the total time of AT and ARI and assessed quantitatively the degree of myocardial ischemia instead of evaluating changes in ST-segment and QT interval (see Fig. 5).

2.1. Cardiac recovery time of normal and patients

It has been suggested that QTc prolongation may be a consequence of an unfavorable balance between sympathetic and parasympathetic activities. Sympathetic predominance accompanied by dispersion of repolarization reflected in QTc prolongation may result in ventricular electrical instability and increase the risk of fatal myocardial infarction. It can thus be speculated that changes in autonomic nervous system (ANS) activity, particularly the sympatho-vagal balance contributes to the prolongation of QTc. We have therefore conducted a series of studies to develop computer algorithms to measure cardiac depolarization–repolarization times and to accomplish the analysis of ECG R–R interval power spectral analysis simultaneously by using the CM5 lead ECG [70]. Additionally, we have applied

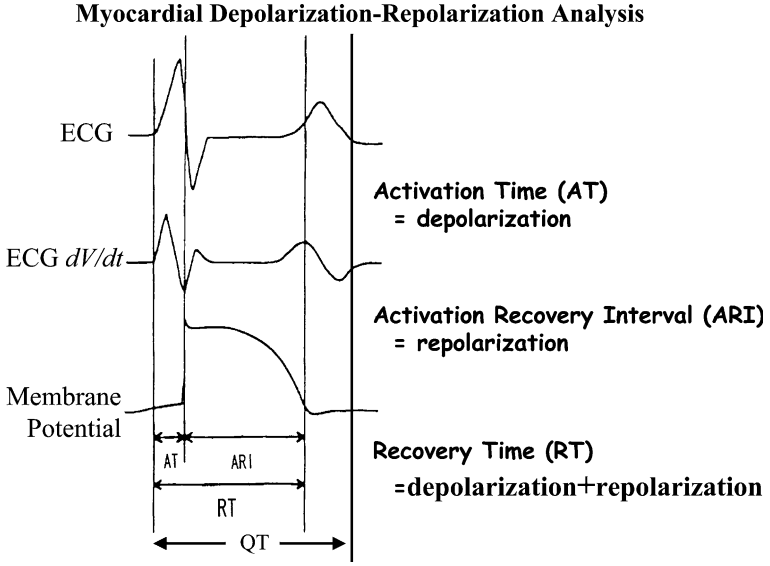

Fig. 5. Electrocardiographic determination of cardiac depolarization/repolarization process.

these techniques to assess diabetic patients with different degrees of neuropathy in terms of cardiac autonomic functions and myocardial depolarization–repolarization processes [34,35,70]. Ten patients with ischemic heart disease (IHD), 30 patients with diabetes mellitus, and 10 control subjects (CON) volunteered for these studies. The patients with diabetes mellitus were further divided into three subgroups according to the severity of neuropathy: patients without any neuropathy (N0), with peripheral neuropathy (N1), and with autonomic neuropathy (N2). Computer-aided cardiac depolarization–repolarization analyses were performed to assess ECG activation time (AT), ARI, and RT.

Figs. 6 and 7 represent a typical set of computer-aided ECG analysis results obtained from a healthy individual and a patient with ischemic heart disease, respectively. Note the remarkable differences in heart rate variability and RT representing the time required for completing cardiac repolarization. ECG R-wave trigger-averaged signals were displayed on the right corner of the figures from which the time of maximal dV/dt of the T waves was determined.

Results shown in Fig. 8 indicated that there were significant increases (prolongation) in RT in N1, N2, and IHD as compared with CON and N0. Thus, our newly implemented computer system could be used for examining the cardiac depolarization–repolarization process in order to study patients with ischemic heart disease and with varying degrees of diabetic autonomic neuropathy.

The hypothesis of adrenergic imbalance as the cause of a long QT interval has been supported by experimental work demonstrating prolongation of the QT interval after either right satellite ganglion ablation or left satellite ganglion stimulation. Schwartz et al. [61,62] suggested that regional sympathetic imbalance involving only a portion of the sympathetic supply might result in long QT syndrome. It is reasonable to conclude that the sympathetic imbalance may have caused the QT interval and RTc prolongation which increased risk for malignant arrhythmias and thereby be responsible for cardiac sudden death. Conversely, increased vagal activity or decreased sympathetic activity decreases vulnerability to ventricular fibrillation or repetitive ventricular response in ischemic animals. Thus, on the basis of many previous studies, autonomic dysfunction is associated with the high-risk patient's susceptibility to ventricular arrhythmias, resulting in sudden death.

2.2. Cardiac autonomic activity assessment

Glowniak et al. [15] did one of the first studies relating heart rate variability to death in cardiac patients. In this study the variance of R–R interval length in short segments of ECG recordings (30 R–R intervals) was calculated. In later studies, 24-h ECG recordings were used to obtain a measure of overall heart rate variability. These studies have also provided that myocardial infarction lowers beat-to-beat heart rate (HR) variability and that diminished heart rate variability is associated with an increased risk for ventricular fibrillation and sudden cardiac death [61,62,70] (also see Figs. 6 and 7). Decreased vagal tone diminishes HR variability and predisposes ventricular fibrillation in animals with

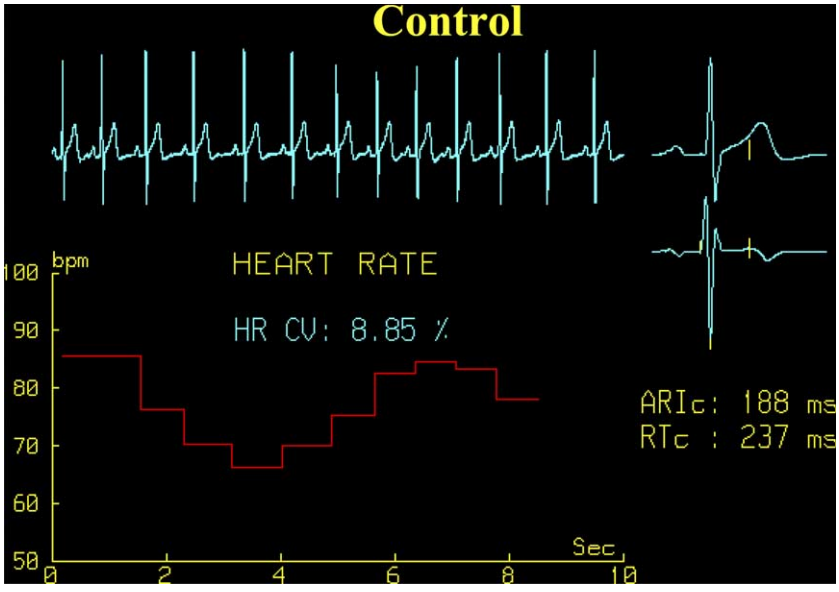

Fig. 6. A typical set of computer out put from a healthy individual showing the raw ECG, R–R interval and trigger-averaged signals for determining cardiac depolarization/repolarization characteristics, i.e., activation recovery interval (ARI), cardiac recovery time (RT), and QT interval, respectively.

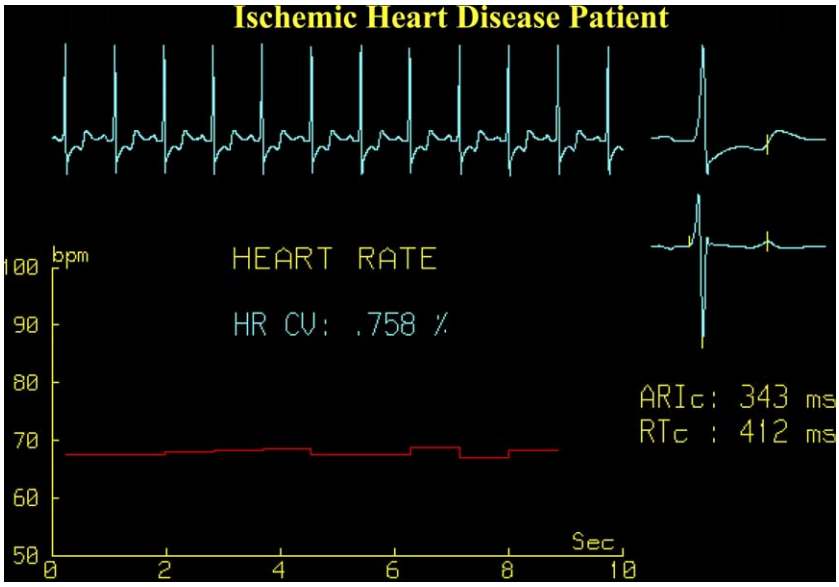

Fig. 7. A typical set of computer out put from a patient with ischemic heart disease showing the raw ECG, R–R interval and trigger-averaged signals for determining cardiac depolarization/repolarization characteristics.

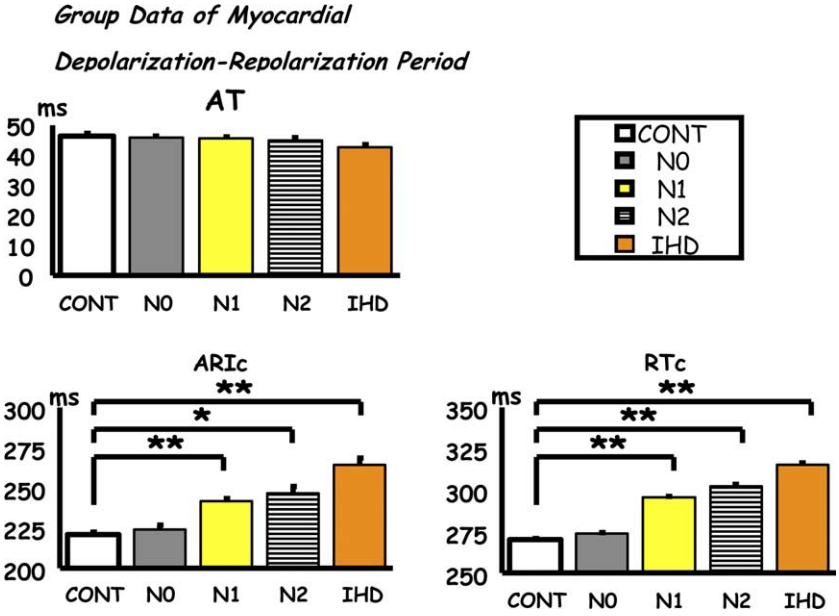

Fig. 8. Group data on myocardial depolarization/repolarization period. Control (CON), diabetic patients without any neuropathy (N0), with peripheral neuropathy (N1) and with autonomic neuropathy (N2) and ischemic heart disease (IHD).

experimental myocardial ischemia. Many studies have demonstrated that increased sympathetic activity during experimental ischemia or infarction promotes ventricular fibrillation [10,11].

Fig. 9 represents our method for cardiac autonomic activity assessment by means of electrocardiogram (ECG) R–R interval power spectral analysis [34,35,70]. The ECG R–R interval, or inter-beat interval of heart rate is determined by the net effect of sympathetic and parasympathetic input. The heart rate variability (HRV) power spectral analysis has been proven as a reliable non-invasive method and has provided a comprehensive quantitative and qualitative evaluation of neuroautonomic function under various physiological conditions [1,2,34,35,48,53,70]. In general, the high-frequencies (>0.15 Hz) of HRV are associated with almost entirely vagal nerve activity and low-frequencies (<0.15 Hz) of HRV might be mediated by both vagal and SNS activities [1,53].

We have examined the possible sympatho-vagal functional differences at rest and during progressive exercise to exhaustion among diabetic patients, normal controls

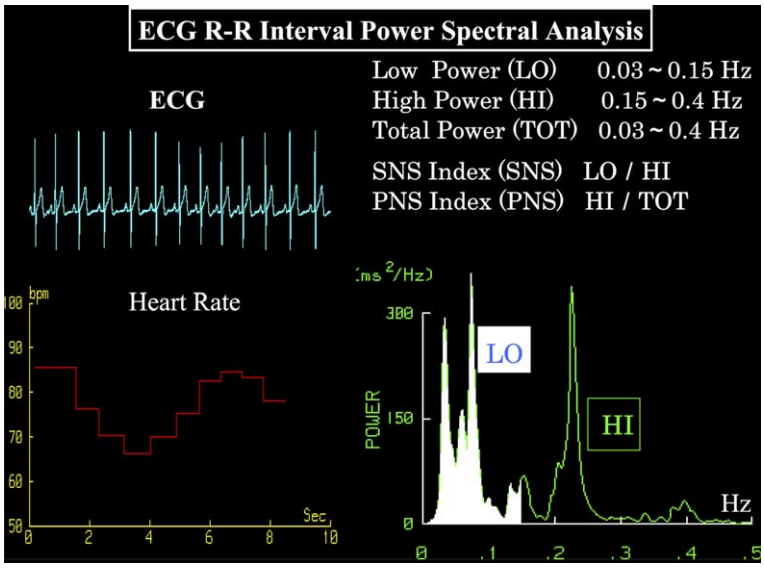

Fig. 9. A schematic representation of our ECG R–R interval power spectral analysis for evaluation of cardiac autonomic activity.

and endurance athletes by means of our computer-implemented ECG R–R power spectral analysis. Since heart rate power between 0.04 and 0.15 Hz was most sensitive and specific in differentiating patients and controls [59], we analyzed low frequency (0.03–0.15 Hz, LO) and high vagal component (0.15–0.4 Hz, HI) by integrating the spectrum for the respective bandwidth. In addition, sympathetic nervous system activity (SNS) and parasympathetic nervous system activity (PNS) indices were calculated as the ratio of LO/HI and HI/TOTAL, respectively.

Fig. 10 shows represents typical sets of raw R–R interval and the corresponding amplitude spectral data obtained from a non-insulin dependent diabetes (NIDDM) patient and a non-diabetic healthy individual (CONT), respectively, during quiet resting. Note that mean heart rate was subtracted from the original R–R interval data, thus only the R–R variability could be directly compared in this figure. It can be readily seen that R–R variability in NIDDM was markedly reduced as compared with the CONT. The corresponding R–R interval spectra also show vast differences in both LO

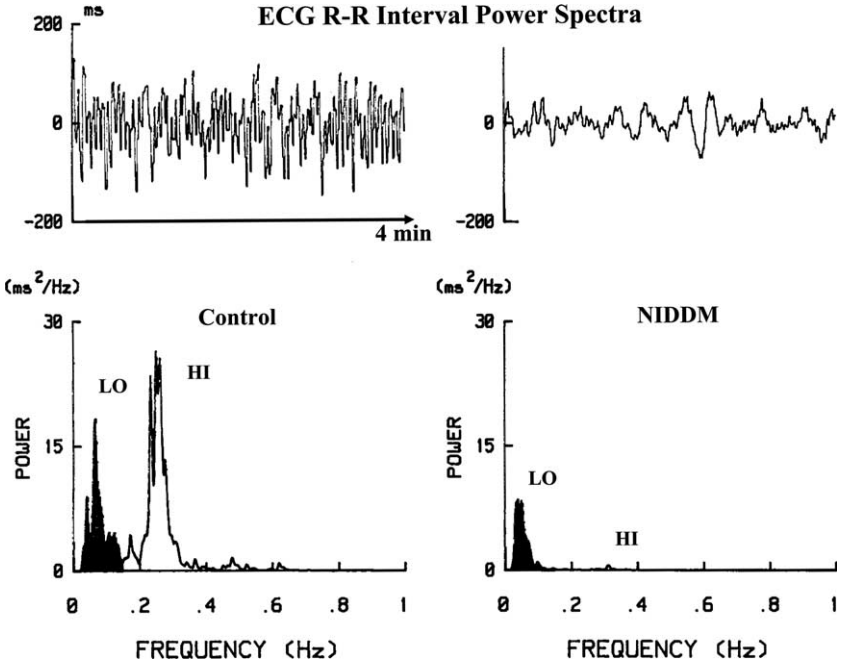

Fig. 10. A typical set of ECG R–R interval power spectra obtained from a patient with non-insulin dependent diabetes and from a healthy individual.

and HI frequency components between these subjects. The most striking feature of the spectra is the contrasting HI vagal component between NIDDM and CONT. These data suggest that a considerable reduction of overall cardiac autonomic nervous system and the withdrawal of the vagal activity might be present in the patients with NIDDM.

Group data indicated that there were significant differences in the HI vagal frequency components among three groups (NIDDM < CONT < ENDR, $p < 0.01$), PNS index (NIDDM < CONT < ENDR, $p < 0.01$) and SNS index (NIDDM > CONT > ENDR, $p < 0.01$), respectively. In the context, the simultaneous assessment of the extent of cardiac parasympathetic nervous activities and imbalance of sympatho-vagal nervous activities found in our studies [34,35,70] may provide the important information of prognosis in the patient's vulnerability for ventricular arrhythmias. In the clinical setting, where coexisting IHD and diabetes mellitus is common, attention must be paid in managing such patients and the assessment of autonomic nervous function.

2.3. Changes in cardiac autonomic activities during smoking and the effects of antioxidant

Sesame seeds have been regarded as a high nutritional value food to promote good health and prevention of aging. Sesamin is one of the lignans existing exclusively in sesame oil. It has recently been demonstrated that sesamin is first transported to the liver where it is metabolized to an antioxidative form, catechol sesamin [46]. We therefore determined the effects of this new antioxidant substance sesamin during acute smoking on cardiac depolarization/repolarization characteristics and cardiac autonomic nervous activities. Nine male college students were tested during acute cigarette smoking after oral administration of placebo or sesamin capsules given at random. Cardiac sympatho-vagal activities and cardiac depolarization/repolarization processes were evaluated continuously by our computer-aided ECG R–R interval power spectral analysis and ECG Q-T interval measurements, respectively. Results indicated that upon cigarette smoking there were significant increases in heart rate and cardiac sympathetic nervous activity together with a significant reduction in the parasympathetic activity. Oral sesamin administration showed a marked suppressive effect upon these changes. Placebo trial also showed a significant prolongation (389 ± 11 to 405 ± 13 ms, $p < 0.01$) in ECG Q-T interval immediately after smoking, which has been known as one of the major risk factors for sudden cardiac death, while sesamin intake prevented such an increase in QT interval (383 ± 4 to 398 ± 4 ms, $p > 0.05$). These data strongly suggest that sesamin can be a useful supplement for reducing the adverse effects of smoking upon cardiac autonomic nervous system. Our subsequent animal experiments clearly indicated that sesamin may enhance lipid peroxidation (LPO) degradation in the liver resulting in the strong protective effects against exercise-induced plasma lipid peroxidation [23].

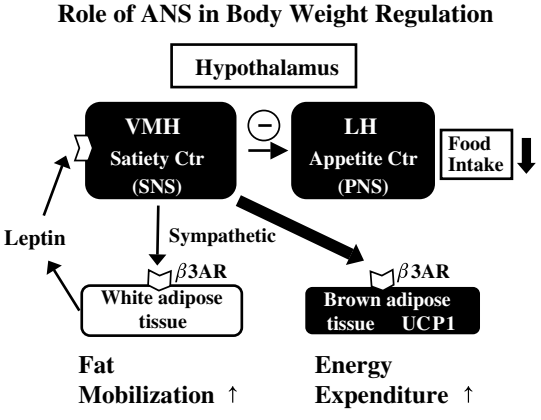

Fig. 11. A block diagram showing a current hypothesis of body weight regulation and fat metabolism.

3. Etiology of obesity and autonomic nervous system

Obesity, a common and important health hazard, is associated with an increased incidence of hypertension, congestive heart failure, diabetes, and cardiac sudden death, as well as an overall increase in mortality rate [54,55]. The causes of most cases of human obesity are still unknown. Recent identification of obese genes (leptin, uncoupling protein (UCP) families and $Trp^{64}Arg$ polymorphism of the β_3-adrenergic receptor) has increased our understanding of the patho-physiology of obesity and related diseases [14,28,57,58,72]. Fig. 11 schematically summarizes current hypothesis explaining the major role of autonomic nervous system activity and its principal components for regulating our body weight.

3.1. Role of autonomic nervous system in body weight regulation

Bray [8] has proposed the MONA LISA hypothesis, an acronym for *M*ost *O*besities k*N*own *A*re *L*ow *I*n *S*ympathetic *A*ctivity indicating that obesity is associated with a relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system.

Since the β_3-adrenergic receptor plays a significant role in the control of lipolysis and thermogenesis in brown adipose tissue through autonomic nervous system (ANS) activity (please see Fig. 11), we first determined the prevalence of the polymorphism in 204 subjects [65,66,69]. Results indicated that the subjects with the variant, even the heterozygotes, demonstrated significantly lower resting ANS activity than normal

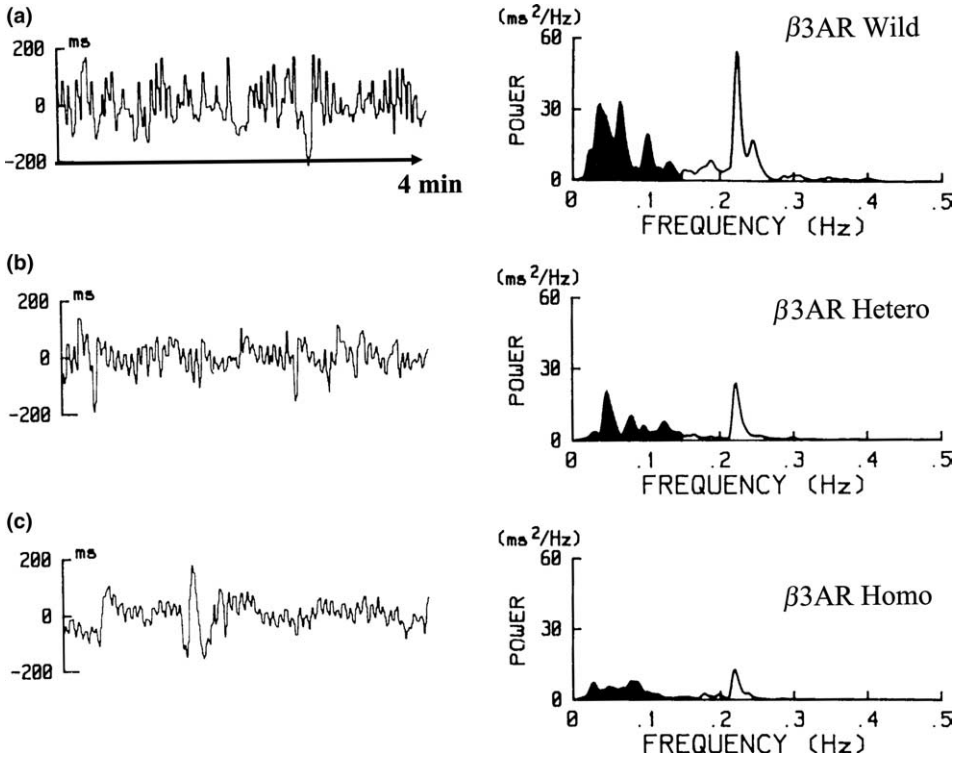

Fig. 12. Autonomic activity among subjects with variant β_3-adrenergic receptor genes.

subjects, whereas the clinical characteristics did not differ between groups (see Fig. 12).

Autonomic responsiveness was then assessed in age and height-matched 27 obese and non-obese women during resting and acute cold exposure (10 °C for 15 min) in an environmental chamber [29]. Prior to this experiment, 6 subjects were studied during pharmacological blockade experiments (parasympathetic muscarinic blocker, atropine and β-sympathetic blocker, propranolol) to examine the effects of autonomic blockade on energy metabolism.

Results indicated that the complete abolishment of the autonomic nervous activity significantly decreased resting metabolic cost amounting to approximately −310 kcal/day, strongly suggesting that ANS does play a significant role in resting metabolism [29]. Plasma leptin was significantly higher in the obese as compared with non-obese group ($p < 0.001$) [30]. There was a highly significant correlation ($r = 892$, $p < 0.001$) between leptin concentration and % body fat [31]. The sympathetic nervous system activity index (SNS) to leptin ratio (sympathetic responsiveness to leptin) was also found to be significantly smaller ($p < 0.001$) in obese as compared to non-obese group [30].

Capsaicin is the major pungent principle in various species of *Capsicum* fruits such as hot chili pepper. It has been shown that dietary supplementation of capsaicin in high fat diets lowered the adipose tissue weight and serum triglyceride concentration in rats due to enhancement of energy metabolism. Our subsequent studies [29,31–33,42,44,45] involving adults and children have demonstrated that upon the acute cold exposure, capsaicin-containing food intake or high fat diets, the obese group demonstrated significantly lower spectral power component associated with thermogenesis as well as significantly lower responsiveness (see Fig. 13).

Our data strongly support the MONA LISA hypothesis and further suggest that obese individuals may show much lower autonomic responsiveness against thermogenic perturbations such as acute cold exposure and diet-induced thermogenesis. Significantly lower sympathetic activities per leptin also dictate that obese women might have a reduced or impaired autonomic responsiveness associated with thermogenic component of the sympathetic nervous system and/or leptin resistance. Our data indicate that regardless of the resting level of sympatho-vagal activities, the reduced sympathetic responsiveness to thermogenic perturbation, which may cause impaired diet-induced thermogenesis and further weight gain, could be an important etiological factor leading to obesity.

3.2. Exercise training and autonomic nervous system

Our previous data suggest that obese children, as well as adults, possess both reduced sympathetic and parasympathetic nervous activities as compared to lean individuals [2,45,71]. Such autonomic reductions associated

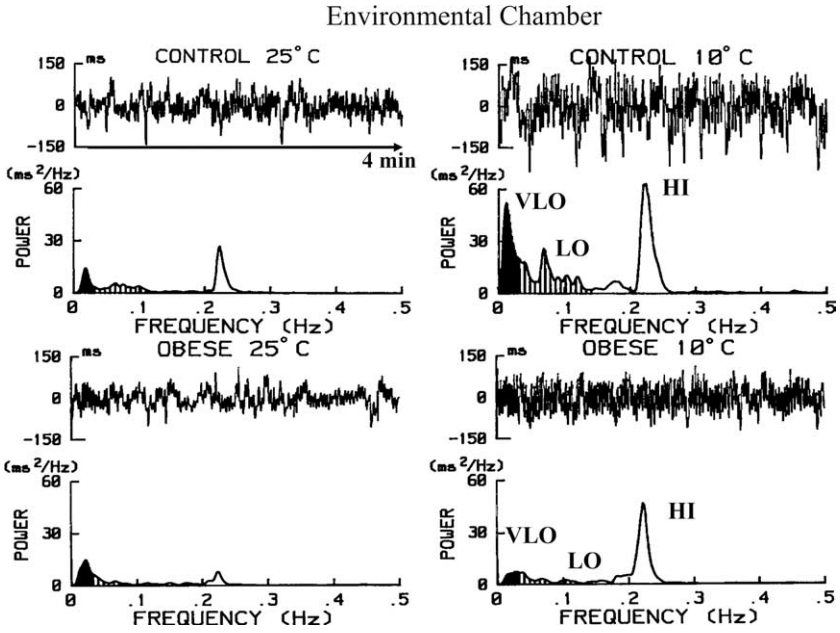

Fig. 13. Comparison of autonomic responsiveness between normal and obese individuals during cold exposure. Note the marked difference in the response of VLO component associated with sympathetic thermogenesis.

with the amount of body fat in an inactive state, might be an etiological factor of the onset or development of obesity. On the other hand, although exercise training not only decreases abdominal visceral fat, but also improves general health, it is recommended for obese people with no contraindications. However, the reduced ANS activity frequently observed in these obese individuals thereby makes them much more prone to develop exercise complications, including malignant arrhythmias, and so exercise prescription should be carefully designed.

We have recently developed a new exercise prescription method based upon cardiac parasympathetic activity [63,64]. To further verify the validity of this new method, we examined the acute effects of aerobic exercise upon sympatho-vagal activities, β-endorphin, atrial and brain natriuretic peptides (ANP and BNP), and EEG. Measurements consisted of beat-by-beat systolic and diastolic blood pressures (SBP and DBP) and cardiac sympatho-vagal activities by means of ECG R–R interval power spectral analysis. Results suggested that moderate exercise could bring about post-exercise hypotension by modulating natriuretic peptides and β-endorphin levels with subsequent changes in autonomic nervous system and brain EEG α-wave activities [36].

We also investigated the effects of long-term physical training on ANS in 305 school children (20 min/day, 5 times/wk for 12 month) [43] and 18 obese middle-aged individuals (30 min/day, 3 times/wk, for 12 wks) [2]. Results indicated that long-term exercise, even for 20 min a day with mild intensity, could significantly improve both the sympathetic and vagal nervous system activities of the children with initially lower HRV. Similarly, the exercise training resulted in a significant decrease in body mass, BMI, and % fat together with a significant increase in the aerobic working capacity (anerobic threshold). Total cholesterol, LDL-C, and leptin were also significantly decreased after exercise training. Our power spectral data indicated that the sympatho-vagal frequency component and total power were significantly increased after training, suggesting a strong possibility of enhanced ANS activities with regularly performed exercise training, particularly the parasympathetic activity, even in the middle-aged individuals.

4. Functional electrical stimulation for health and disease

4.1. Electrical stimulation vs. voluntary contraction

Electrical stimulation (ES) produces skeletal muscle contractions as a result of the percutaneous stimulation of the peripheral nerve. Clinically, the use of ES has been shown to potentially improve or compensate for disadvantages in disabled or chronic patients with physical inactivity. In fact, ES of skeletal muscles might not only improve cardiovascular function for tetra or paraplegics, but may also increase the strength and endurance of their paralyzed muscles during daily activity such as wheelchair locomotion or body transfer [12,24]. In addition, previous animal experiments have shown that glucose transport activity is considerably higher in Type II than Type I fibers when ES is employed [25,56].

Unlike the orderly recruitment of motor units (MUs) during low intensity voluntary exercise in which Type I slow-twitch fibers are utilized first [16,39,40], during ES, large and fatigable fast-twitch motor units (MUs) with glycolytic fibers are activated first. Because of their larger axons, which in turn have much lower electrical resistance for a given externally applied electrical current [9,20,68], large fast-twitch MUs would be activated before slow-twitch MUs, suggesting "reversed size principle" of MUs recruitment by ES. Our most recent study [20] has clearly demonstrated that fast MUs are selectively activated during ES.

The selective activation of fast MUs by ES would be quite useful in preventing and treating patients with diabetes and chronic diseases with subsequent muscle atrophy leading to bed-ridden conditions. ES has been traditionally employed for muscle strengthening, maintenance of muscle mass and strength, and restoring muscular functions following stroke or spinal cord injury. Exercise increases glucose uptake by the translocation of GLUT-4 glucose transporters, similar to the action of insulin, but though independent mechanisms [17,22]. It is quite reasonable to assume that ES may become a better approach to enhance the glucose transport activity in skeletal muscle. This low intensity ES without requiring vigorous voluntary exercise ensures the activation of Type II fibers with subsequent enhancement of post-stimulation glucose uptake, particularly for those individuals who are unable to exercise due to orthopedic problems or other complications.

We have therefore performed a series of experiments [18,19] to establish the most optimal ES frequency, intensity, duration, and pattern and to directly measure oxygen consumption and whole body glucose uptake by means of glucose disposal rate (GDR) in hyperinsulinemic–euglycemic clamp, respectively. In the first experiment, efforts were made to determine the optimal stimulation frequency that would induce the highest oxygen uptake during a 20-min sustained ES to the right quadriceps muscle. The polarity (monophasic vs. biphasic) and stimulation-rest duty cycle were also examined. In addition, the knee extension force measurement was simultaneously made during these various patterns of muscle surface stimulations. It was found that either lower or higher than 20 Hz stimulation frequency with 1 s on 1 s off duty cycle resulted in much lower oxygen consumption and the total amount of accumulated force. In fact stimulation at 60 Hz with identical ES pattern showed marked force loss towards the end of ES due to impaired neuromuscular transmission or membrane excitation, i.e., high frequency fatigue [13,37,38]. We therefore adopted the stimulation pattern with 20 Hz frequency and 1 s on–off duty cycle with biphasic polarity as the optimal conditions for ES and used this protocol in the subsequent invasive study.

For the subsequent experiment, 8 male college students volunteered for the invasive hyperinsulinemic–euglycemic clamp measurement. The subject was in the supine position with both knees extended and surface electrodes were placed over the motor points in the proximal and middle portion of the thigh. Both quadriceps muscles were then simultaneously stimulated to induce isometric muscle contractions for a period of 20 min. Stimulation consisted of square-wave biphasic pulses of 0.2 ms duration at 20 Hz. Stimulator output was limited to 80 volts for painless muscle contraction. Oxygen consumption determined by respiratory gas exchange analysis was rapidly increased by approximately 2-fold in response to muscle stimulations (3.2 ± 0.1 to 5.7 ± 0.1 ml/kg/min (means ± SE), $p < 0.05$). The increase in oxygen consumption was maintained throughout the stimulation period, and then returned to the baseline level immediately after the cessation of the stimulation. Similarly, whole body glucose uptake determined by glucose disposal rate (GDR) in hyperinsulinemic–euglycemic clamp was acutely increased in response to electrically-induced contractions from 7.2 ± 0.4 mg/kg/min to 9.7 ± 0.9 mg/kg/min ($p < 0.01$). Furthermore, GDR remained elevated during the post-stimulation period for at least 90 min (0–30 min, 10.1 ± 0.6; 30–60 min, 10.0 ± 0.4; 60–90 min, 11.4 ± 0.8 mg/kg/min, $p < 0.01$ vs. baseline) while the steady-steady insulin concentration during clamp was within the physiological range for all the subjects and also sufficient to suppress endogenous glucose production (~70 U/ml). These results strongly suggested that, similar to voluntary exercise, involuntary muscle contraction leads to substantial enhancement of energy and glucose utilization in humans (see Figs. 14 and 15).

In the second experiment we further examined the acute metabolic effects of ES to lower extremities in comparison with voluntary cycle exercise (VE) at an identical intensity. In eight male subjects, lying in the supine position, both lower leg (tibialis anterior and triceps surae) and thigh (quadriceps and hamstrings) muscles were sequentially stimulated to co-contract in an isometric manner at 20 Hz with a 1-s on–off duty cycle for 20 min. Despite of the small elevation of oxygen uptake by 7.3 ± 0.3 ml/kg/min during ES, the blood lactate concentration was significantly increased by 3.2 ± 0.3 mmol/l in initial period (5 min) after the onset of the ES ($p < 0.01$), whereas VE showed no such changes at an identical oxygen uptake (7.5 ± 0.3 ml/kg/min). ES also induced enhanced whole body carbohydrate oxidation as shown by the significantly higher respiratory gas exchange ratio than VE ($p < 0.01$). These data indicated increased anerobic glycolysis by ES. Furthermore, whole-body glucose uptake determined by GDR during euglycemic clamp demonstrated a significant increase during and after the cessation of ES for

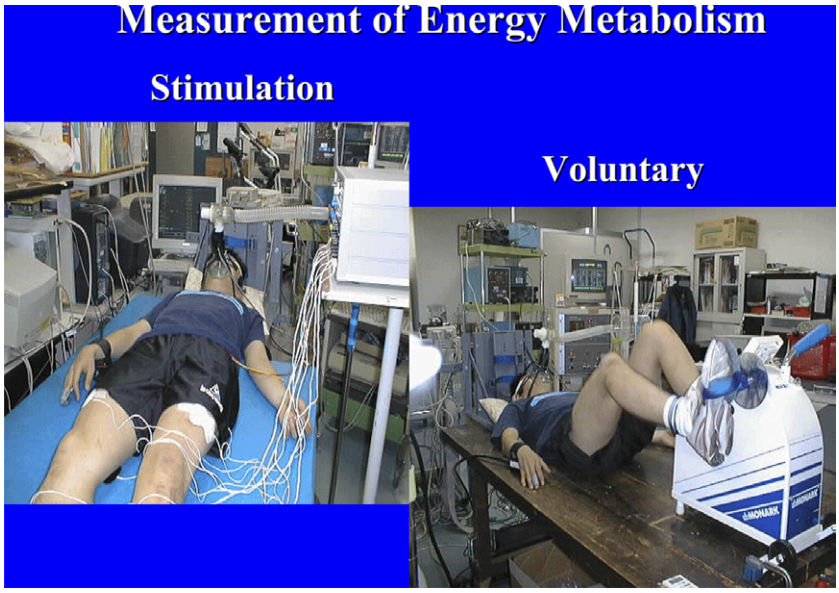

Fig. 14. Pictures showing experimental setup for performing electrical stimulation and voluntary exercise at identical energy consumption.

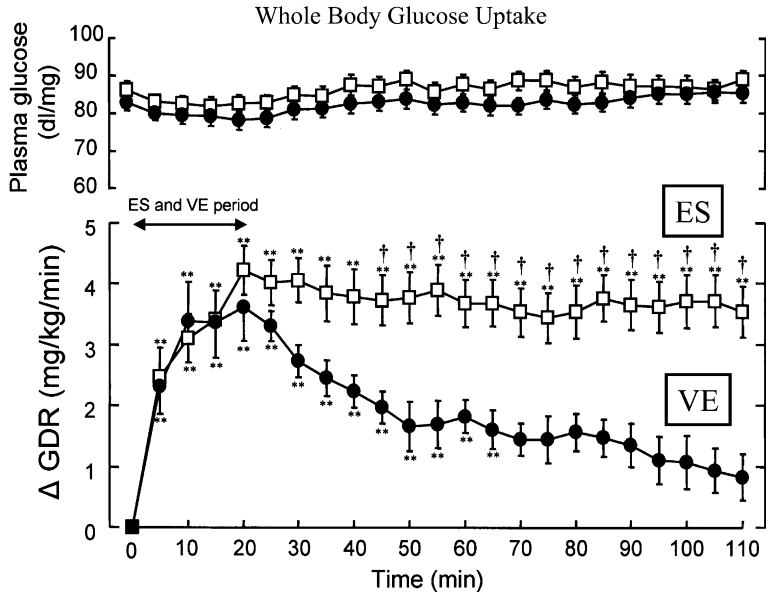

Fig. 15. Time course of changes in whole body glucose uptake during electrical stimulation and voluntary exercise.

at least 90 min ($p < 0.01$). This post ES effect was significantly greater than that of the post VE period ($p < 0.01$). These results suggested that ES can substantially enhance energy consumption, carbohydrate oxidation, and whole body glucose uptake at low intensity of exercise. We therefore concluded that ES may become a useful modality that could enhance, through the insulin-independent mechanisms, glucose uptake in skeletal muscle of those patients with peripheral insulin resistance, such as non-insulin-dependent diabetes mellitus and/or chronic patients with progressive muscle atrophy.

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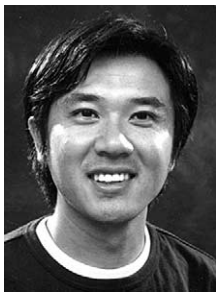

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