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Physiologic Responses to Vigorous Exercise in Older Men

By
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B.S. (University of California, Davis) 1977
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THESIS

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Chairman Date

Amanda Kramer 4/29/87

J. A. Brooks 4/30/87

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

REVIEW OF THE LITERATURE

Many benefits are attributed to exercise, including the promotion of a healthier, longer life and a more beneficial cardiovascular profile (1). With increased emphasis placed on endurance activity and its avid participation by older generations, it is of utmost public health importance to understand the physiology of vigorous exercise among an elderly, coronary-prone population, and more specifically, the physiology of exercise-related morbidity, otherwise referred to as sudden cardiac death.

Sudden death (SD) is a broad term commonly defined in the literature as death within 24 hours from natural causes of an individual who has not been restricted by ill health to home, hospital, or other institution and who has been leading a normal life in the community until 24 hours prior to the onset of the fatal event (2). It is estimated that the yearly incidence of sudden death is approximately 350,000 each year (3), the incidence increasing two-fold each decade after age 45 (4).

The definition implies correctly that SD can occur to anyone during any activity. The Framingham study (3) followed community members for 20 years and

found their incidence of sudden death to be inversely proportional to their amount of daily exercise and physical exertion. However, they found when SD did occur, it occurred with greater frequency in a setting of physical activity. Other studies (5,6) found the incidence of SD to be higher during high intensity exercise than at other times. These studies are in agreement with several others that implicate the risk of SD to be increased by exercise (7,8,9).

The occurence of sudden death during and post exercise is thus widely recognized and well documented (10,11,12). These studies show that the majority of cases occur in males and are cardiovascular in origin (12). The timing of such events occurs with equal frequency during maximal exercise as during the immediate recovery period (13).

Ventricular fibrillation is the fatal terminal event of sudden death (14) particularly in exertion-related cases, and is commonly superimposed upon a condition of chronic, unrecognized coronary atherosclerosis (7) and acute myocardial ischemia. The factors implicated as contributing to this abnormal electrical conduction include ischemia, central and peripheral nervous system stimulation (i.e. catecholamines), vasospasm, and prostaglandins.

As a first step of several to elucidate the physiologic mechanism of sudden cardiac death during

high intensity exercise, this work attempts to define the physiologic responses to vigorous exercise, specifically, the *frequency of ventricular arrhythmias* and the plasma levels of *catecholamines* among healthy older men during and immediately after a 10 KM run. Both the sudden death and exercise physiology literature will be reviewed with respect to each of these parameters below.

1. *Frequency of ventricular arrhythmias*

The risk of sudden death varies widely in relation to risk factors commonly identified for coronary heart disease (CHD), and includes electrocardiographic (ECG) abnormalities. A six-fold increase in the incidence of SD has been reported in subjects demonstrating abnormal ventricular rhythms on routine ECG studies (3).

As aforementioned, ventricular fibrillation is the common underlying event in exercise-related sudden cardiac death. Exercise may precipitate myocardial ischemia and infarction in certain persons by reducing myocardial oxygen supply and concommitantly decreasing the resting phase of diastole and perfusion to the heart, creating a situation of oxygen deficiency in subendocardial tissues (11).

There is little agreement among experts on the mechanism of fibrillation. In general it is believed ischemia promotes a surge of catecholamine activity,

locally and systemically, which in turn promotes a condition of electrical instability within the myocardium and asynchronous firing of electrical impulses (15).

Abnormal electrical circuitry is first evidenced by premature ventricular depolarizations, accelerated idioventricular rhythms (heart rhythms arising from the ventricle alone dissociated from atrial conduction) and ventricular tachycardia. These events aggravate ongoing ischemia, noted on ECG tracings as ST segment depression (≥1 mm depression of the ST interval 80 ms after the J point), and prompt the likelihood of ventricular fibrillation.

Premature ventricular complexes (PVC's) have been noted to occur with greater frequency in men, to increase with age and with ischemia detected on ECG's. (3). Data from Framingham demonstrated a three-fold increase in risk of sudden death in those individuals presenting with PVC's on routine studies as compared to those without any PVC's (5). A gradation of severity exists even within this category--specifically, high frequency premature ventricular complexes of multifocal origin and short coupling intervals defining the most serious expression of these complexes, while occasional unifocal PVC's appear to be of lesser consequence.

As with the prevalence of CHD, the prevalence of cardiac arrhythmias noted in apparently healthy well-

trained men increases with age. McHenry (16) demonstrated the incidence of PVC's and supraventricular premature complexes to increase progressively among 650 men in the Indiana State Police Force, in age groups 25-34 years old, 35-44 years old, and 45-54 years old during maximal exercise testing. Pantano (17), in a study of 60 well conditioned men and women runners (aged 16-68 years old), found treadmill testing to underestimate both the frequency and the grade of ventricular arrhythmias when compared to Holter monitored outdoor running.

2. *Plasma catecholamines*

Exercise precipitates a variety of alterations in blood flow, metabolic and hormonal processes, mediated in large part by sympathoadrenal catecholamine release. Catecholamines, norepinephrine (NE) and epinephrine (EPI), redistribute blood flow away from splanchnic organs and resting skeletal muscle to working muscle. Additionally, catecholamines have metabolic functions which include lipolysis, glycogenolysis, and gluconeogenesis and cardiac functions.

Mediated primarily by beta-adrenergic receptors, catecholamine actions on the myocardium are both inotropic and chronotropic, serving to increase automaticity, force of contraction, heart rate, and

conduction velocity in His-Purkinje tissues (specialized conducting tissues in the A-V nodal region) and to decrease A-V nodal refractoriness. It is believed that it is this effect of catecholamines on cardiac tissue during exercise that predisposes, in a hypoxic state, to abnormal ventricular rhythms.

It is known that catecholamines increase with intensity of exercise (18,34). NE and EPI concentrations were shown by Hartley to increase in 12 college football players, from a resting condition (172 ± 18 pg/ml and 40.9 ± 9 pg/ml respectively; mean ± SEM) progressively with hand-grip exercise, standing for 10 min, and finally reaching highest values (3985 ± 670 pg/ml and 1080 ± 321 pg/ml respectively) with 12 minutes of supramaximal cycle ergometric testing (19). Kraemer et al (20) has shown NE and EPI concentrations to increase progressively in healthy college-age males performing bicycle ergometry testing at 28%, 54%, 83% and reaching maximal levels at 100% of VO_2 max.

NE and EPI concentrations progressively declined from peak levels during a 15 minute recovery period in this same study (20). In another study, NE concentrations in 5 healthy young male trained subjects were found to peak at 1 minute into recovery, after 5 minutes of bicycle ergrometry testing at 78% of VO_2 max, and declining progressively thereafter during the next 30 minutes of recovery (21). As can be noted, most

previous investigations of plasma catecholamines have focused on young to middle-aged men, with exercise consisting of relatively brief periods of activity. With this level of activity, plasma NE has been shown capable of increasing 16-fold above baseline values.

It is known however, that basal plasma NE concentrations are elevated in healthy elderly subjects (63-85 years of age) when compared to younger (30-40 yrs of age) subjects and this elevation is believed to be due to increasing rates of NE entry into the circulation without changes in the rate of NE production (22).

In one of the very few studies done on catecholamine levels in elderly vs. younger subjects during exercise, Palmer (23) demonstrated NE to be considerably higher at rest (twice) and during five minutes of isometric exercise (one and one-half times) in an older group of men and women (52.9 ± 0.9 years).

Clinical evidence demonstrates plasma catecholamine levels are greatly increased in patients after an acute myocardial infarction (24), plasma NE levels reaching approximately 1000-1500 pg/ml, which is considerably lower than NE values noted in maximal exercise situations. NE levels immediately preceeding a myocardial infarction are unknown.

In myocardial infarction (MI) patients, treatment with beta-adrenergic blockers is a common

practice in intensive coronary care units. This treatment has been reported to decrease the rate of reinfarction and retard the development of the infarct in threatened myocardial infarction (24). In one other study of 6 post-MI patients (mean age= 63 yrs), blood was drawn within 30 minutes of cardiac arrest. It was found that plasma catecholamine levels were significantly raised to levels (28.6 nmol/l) that have been recorded after cardiac arrest (24.7 nmol/l), but were much higher than those found post-MI (5.6 nmol/l) (25). The authors suggest high catecholamine levels may be an early warning signal of arrest.

In summary, a thorough review of the literature suggests the following limitations in studies addressing catecholamine responses to vigorous exercise carried out to date: 1) early work cited less-accurate urinary catecholamine concentrations due to lack of techniques to measure NE and EPI in plasma, 2) men and women were commonly co-investigated, 3) elderly populations were relatively unstudied, 4) subjects were often tested in a non-fasting state; many substances such as chocolate, coffee, tea and cocoa can alter catecholamine response, 5) responses to endurance activity were infrequently studied vs. isometric or brief amounts of activity, and 6) the recovery period post-vigorous exercise also has been infrequently considered.

PURPOSE OF INVESTIGATION

The physiology of exercise-related morbidity, which is of considerable public health importance, is not well understood and relatively unstudied in older men.

The purpose of this investigation is to examine potential factors implicated in the literature to be involved in the pathogenesis of sudden cardiac death, specifically, ventricular arrhythmias and plasma catecholamines during an exercise bout that is comparable to practiced exercise regimens.

Two main hypotheses are put forth in this thesis:

(1) *Arrhythmias* will occur with greater frequency in older versus younger male runners during and immediately post a vigorous exercise bout.

(2) *Plasma catecholamine* levels will be higher in older versus younger male runners during and immediately post a vigorous exercise bout.

To accomplish the above, two groups of runners were selected to participate in a cross-sectional study design in which frequency of arrhythmias was observed, and plasma catecholamines were sampled at rest, at

various timepoints during a 10 KM run on a treadmill and during a 20 minute recovery period via an indwelling catheter.

MATERIALS AND METHODS

1. Subjects.

Twenty-two healthy male runners, twelve 55-65 year olds and ten 20-30 year olds, participated in this comparison study of responses to vigorous exercise. The older subjects were *recruited* via a newsletter sent to The 50-Plus Runners Association, a club of active older runners, via flyers distributed at 2 local runs (Appendix A), and by an article placed in the Campus Daily, a local Stanford newspaper (Appendix B). The younger runners were also recruited via flyers at these runs along with posters placed around the Stanford campus and direct solicitation to local running clubs.

All subjects were nonsmokers in generally good health, and free of known cardiovascular disease. They were within 10% of Ideal Weight (as assessed by Metropolitan Life Insurance Company charts). In addition, all men had run habitually as their main form of exercise and entered at least two 10 Kilometer (KM) races in the last year with completed times in the younger group of 35-41 minutes and in the older group of 45-51 minutes. These times corresponded respectively to above average runners in each age

group, representing running times within 15-30% of the fastest average time in each age group of twenty 10 KM races in the Bay Area in the last year. All men also were free of orthopedic complications and did not use any medications.

Following initial contact by newsletters or flyers, potential participants phoned SCRDP, Stanford Center for Research in Disease Prevention, and were queried regarding the above mentioned *exclusionary criteria* and assessed for further continuation and screening (Appendix C). If determined eligible by phone contact, potential candidates attended an orientation visit at SCRDP, during which further information regarding the study was disseminated and forms were completed which included mailing, demographic, physical activity, and medical history information (Appendix D-G). Based upon satisfactory eligibility and continued interest, subjects were signed up for a preliminary screening visit. All signed consent forms prior to this visit and were given a copy of the Medical Research Subjects' Bill of Rights prior to the start of any testing (Appendix H). Participation was totally voluntary; no monetary compensation was given.

The *screening* visit was conducted in the SCRDP clinic facility in the morning, with subjects fasting for 12-16 hours, and having completed no vigorous

physical activity that morning. During this visit, height and weight were taken on medical scales; blood pressure was measured three times, following a 10 minute resting period, with heart rate measured between the second and third readings; venipuncture for determination of lipids in plasma which was centrifuged, refrigerated and measured with 48 hours; and urine was assessed for glycosuria by a urine dipstick (Appendix I). If the above testing revealed blood pressure values of less than 155/95, total cholesterol less than 300 mg% , plasma triglyceride less than 500 mg% and absence of glucose in the urine, the subject was allowed to proceed.

This project was approved prior to its inception by the UCB Committee for the Protection of Human Subjects as well as the Stanford University's Human Subjects' Committee.

2. Experimental Design

The duration of testing for this study was from late August to December 1986, this time period dictated by clinic and treadmill space availability. The subjects were instructed to continue their normal exercise and food consumption routines for the duration of their testing. All measurements taken were expected to be indications of the individual's state at the time of the experiment. No change in any parameter over

the study period was expected. During the course of the study, two main tests were performed on each subject: (1). VO_2 max treadmill testing and (2). 10 KM treadmill testing. Each of these tests occurred on separate mornings and will be described below.

(1). *VO_2 max testing* with oxygen uptake was done to determine individual fitness levels. Each participant came to the clinic in running attire following a 12-16 hour fast and no vigorous activity undertaken that morning. Height and weight were measured as were *resting* blood pressure and 12-lead resting electrocardiogram by a registered nurse and medical doctor prior to beginning the test. A heart and lung exam was also performed on each subject by the RN. Each subject was allowed a 10 minute stretch and outdoor warm-up period prior to starting the test. Upon clearance by the RN and MD, each subject was hooked to oxygen uptake equipment and was brought to a speed determined to be a comfortable running pace by the subject. This speed remained constant throughout the duration of the *exercise* test. The workload was increased at two minute intervals by increasing the grade of the treadmill 2.5% until a maximal (symptom limited) effort was achieved. During this exercise phase, ECG's were continuously monitored by a registered nurse and blood pressures were taken every 2 minutes, as was an assessment of RPE (relative

perceived exertion) by the subject. Immediately upon cessation of the test, the treadmill grade was brought to 0% and blood was drawn in the supine position for determination of a maximal effort related catecholamine sample. Subjects were then followed for an additional 20 minute *recovery* period during which BP was monitored each 2 minutes as well as continuous monitoring of ECG's.

Following satisfactory completion of VO_2 max treadmill testing, each subject returned to the SCRDP clinic facility for 10 KM treadmill testing, again in running attire following a 12-16 hour fast and no vigorous activity performed the morning of testing.

(2) *10 KM treadmill testing* again involved 3 phases: resting, exercise and recovery. During the *resting* phase, height and weight measurments were taken, followed by an insertion of an 18-guage angiocatheter into the left basilic, cephalic or median vein of the forearm (whichever was deemed largest and most accessible) by the RN and was appropriately secured for the 10 KM run. Immediately after placement, the line was flushed with 20 units of heparin and was kept patent with 10 cc of normal saline to prevent local coagulation. The subject was instructed to rest quietly in a supine position (the room was darkened and a warm blanket placed over subject) for the next 30 minute period, at the end of

which a baseline sample of catecholamines were drawn (B_1).

Each subject was then prepared for 12 lead electrode placement. Prior to beginning the actual test, resting blood pressures and a resting 12-lead ECG were taken in a standing position and were evaluated by RN and MD. Oxygen uptake was not measured during the 10 Km run, allowing verbal communication throughout the run. The initial 10 minutes of *exercise* once the treadmill was started, was not counted into total 10 KM time and was designated as a "warm-up" period. Actual 10 KM time was based upon each individual's most recent and performable 10 KM time. The treadmill speed was thus computed to correspond to this total 10 KM time. Adjustments in speed were allowed at 1/4, 1/2 and 3/4 time points only. The grade was constant for all participants at a 2.5% level. Blood pressures were measured every 4 minutes throughout the run and heart rates and ECG's were continuously monitored by an RN. At the midpoint of the run, each subject was brought to a fast walk (approximately 4 mph) and was given water ad-lib. This period of time, which averaged approximately 3 minutes was not counted into total 10 KM time. In addition, a fan was placed in front of the treadmill for cooling purposes. Blood samples were drawn immediately prior to beginning (B_2), at midpoint (MP) and endpoints (EP) of the run. The exercise

portions were completed satisfactorily by all 22 participants.

Once the 10 KM distance had been run, the treadmill speed was reduced to 2.5 mph (a walking pace) for the next 20 minutes. Blood pressure was taken every minute for the first 10 minutes in *recovery* and thereafter, every 2 minutes. Heart rate and ECG's were again continuously monitored. Blood samples were drawn from the catheter at 1, 3, 5, and 10 minutes (R-1, R-3, R-5, R-10) in recovery. All 22 subjects satisfactorily completed the recovery portions of the test. In a few cases (n=5), mechanical failure of the catheter occurred during the run, necessitating alternate blood sampling in recovery. These few runners immediately upon finishing the run, hopped off the treadmill and laid supine while the nurse inserted a butterfly needle into an accessible arm vein for drawing the recovery blood samples. Completion of this test concluded each participants involvement in the study.

3. Methods of Analysis

Fasting blood was drawn at the following times:

initial screening	for lipid determination
VO-2 max test (at max. effort)	for catecholamines
10 KM run	for catecholamines

Blood drawn for *lipid determination* was done via venipuncture of the median antecubital vein. Blood was collected into 15 ml vacutainers containing ethylenediaminetetraacetic acid (EDTA) and was spun in a refrigerated Beckman model TJ-6 centrifuge (0° C) at 2000 rpm for 20 minutes. Samples were stored in a refrigerator and assayed within 48 hours by Indirect Beta Quantification. This test yields plasma concentrations of triglyceride and total cholesterol. These tests were carried out in the Stanford Lipid Laboratory. Cholesterol and triglycerides were determined by enzymatic procedures on the Abbott Analyzer (26).

Catecholamine samples (8 ml) drawn at maximal effort during the *VO-2 max test* were drawn into one 10-ml plain sterile vacutainer which was immediately transferred to a tube containing EGTA (ethylene glycol tetraacetic acid) and reduced glutathione, ph 6-7. These tubes were then spun in a refrigerated centrifuge for 20 minutes at 2000 rpm and stored at -80°C in a 5.0 ml Wheaton vial for future analysis.

Catecholamine samples (8 ml each draw) drawn during the *10KM treadmill test* were drawn into 10 cc syringes via the angiocatheter at the following timepoints: resting supine after 30 minutes (B_1), standing prior to 10K run (B_2), midpoint (MP), endpoint

(EP), and at R-1, R-3, R-5, and R-10 minutes in recovery. The 2.2 cm. line attached to a 3-way stopcock for easy sampling, was flushed with heparin and normal saline periodically to avoid clot formation. The first 2.5 cm of each draw was discarded before the sample was collected. Once collected, catecholamine samples were immediately placed into tubes containing EGTA and reduced glutathione, ph 6-7. All samples were kept on ice until centrifugation in a refrigerated centrifuge for 20 minutes at 2000 rpm. All eight catecholamine samples were stored at -80°C in 5.0 ml Wheaton vials, along with the maximal catecholamine sample drawn during VO-2 max testing. Catecholamine determinations were made during March, 1987 by the method of Mefford et al (27). Plasma was thawed at room temperature and subsequently extracted with alumina and perchloric acid and analyzed in triplicate for epinephrine and norepinephrine by high pressure liquid chromatography (HPLC), utilizing an ESA Coulometric Detector.

4. Statistics

Data analysis focused on the evaluation of the primary goal of testing whether there were significant group differences between older and younger men. Students' two-sample t tests were employed to test whether there were any significant differences between

plasma catecholamine responses to exercise (28). Two tailed t tests were also employed to determine differences between groups for the following parameters: age, height, weight, BMI (body mass index), resting heart rate, 10 KM Personal Records, miles run/week, VO-2 max, maximal HR, and lipids. Frequency of arrhythmias was compared for older and younger men using Fishers exact test for a 2 x 2 contingency table (29).

RESULTS

1. *Descriptive Characteristics.*

The descriptive characteristics of the runners, older and younger are shown in Table 1. The term "descriptive characteristics" used here includes the following measurements: age, height, weight, BMI (body mass index), HR (heart rate)-both resting and maximal, 10 KM PR (personal record), miles run/week and VO_2 max. This term will be referred to throughout the results and discussion sections of this text, and is to represent the above listed measurements.

There were no significant differences in height, weight, BMI, resting HR or miles run/week.

As expected, 10 KM PR times were significantly faster ($P<0.001$) in the younger runners (36.75 min. $\pm$ 2.56) than the older runners (44.32 min $\pm$ 2.80). Aerobic capacity as determined by VO_2 max was signficantly higher in the younger runners (64.35 ml/kg/min $\pm$ 5.44) than in the older runners (51.33 ml/kg/min $\pm$ 5.03). This too was expected. Maximal HR (taken at maximal effort during aerobic capacity testing) was again significantly higher in the younger runners (187.6 bpm $\pm$ 7.98) versus that found in the

TABLE 1

Comparison of Descriptive Characteristics
Between Older and Younger Runners

	Older Runners (n=12)	Younger Runners (n=10)	Difference	Significance[1]
	(mean ± SD)	(mean ± SD)	(mean ± SE)	(P)
Age (years)	58.00 ± 2.83	26.30 ± 1.63	31.70 ± 0.97	≤0.001
Height (cm)	177.00 ± 4.72	180.20 ± 6.38	- 3.20 ± 2.43	NS
Weight (kg)	72.90 ± 4.64	74.10 ± 4.85	- 1.20 ± 2.04	NS
BMI (kg/m^2)	23.42 ± 1.44	22.85 ± 1.34	0.57 ± 0.59	NS
HR (resting, bpm)	52.66 ± 8.50	58.60 ± 9.43	- 5.94 ± 3.86	NS
10 KM PR (min)	44.32 ± 2.80	36.75 ± 2.56	7.57 ± 1.14	≤0.001
Miles run/week	30.00 ± 9.91	33.70 ± 15.35	- 3.70 ± 5.63	NS
VO_2 max (ml/kg/min)	51.33 ± 5.03	64.35 ± 5.44	-13.02 ± 2.25	≤0.001
HR max (bpm)	167.00 ± 7.40	187.60 ± 7.98	-20.60 ± 3.31	≤0.001

[1] 2 sample t-test

older runners (167.0 bpm ± 7.40).

The older runners ran the 10KM distance at 85.95 ± 9.76% of their VO_2 max, which was not significantly different from the younger runners, who ran 10 KM at 84.61 ± 8.18% of their VO_2 max. Older runners did take longer to run the distance as expected, with a mean time of 50.49 ± 1.69 minutes, while the younger runners covered the same distance in 39.61 ± 2.37 minutes ($P \leq 0.001$).

2. *Frequency of ventricular arrhythmias.*

Table 2 presents the incidence of abnormal cardiac conduction during 10 KM treadmill testing and in recovery. In the category of ventricular arrhythmias, the frequency of premature ventricular contractions (PVC's) was significantly greater ($P=0.043$) in the 55-65 year old runners; approximately 55% of this group experiencing six or greater PVC's during the test and recovery, as compared to only 10% of the 20-30 year old runners experiencing 6 or greater PVC's. Ninety percent of the younger runners demonstrated 0-5 PVC's as compared to 45% of the older group falling into this category of 0-5 PVC's during the test and recovery. All PVC's were unifocal and singular with two exceptions; 1) one older runner who demonstrated both multifocal singular PVC's and multifocal couplets at rest and during the run and 2) one younger runner who had only

TABLE 2

Incidence of Ventricular Arrythmias and ST Segment Depression Observed During a 10 KM Treadmill Run and in Recovery in Older and Younger Runners

		Ventricular Arrythmias					
		PVC's		Fusion Beats		Ventricular Tachycardia	ST Segment Depression (≥1 mm)
Age group	n	Frequent (≥ 6)	Occasional (0-5)	Frequent (≥6)	Occasional (0-5)		
Older runners (55-65 years old)	11	6 (54.5%)	5 (45.4%)	3 (27.3%)	8 (72.7%)	0 (0.0%)	5 (45.4%)
Younger runners (20-30 years old)	10	1 (10.0%)	9 (90.0%)	0 (0.0 %)	10 (100.0%)	0 (0.0%)	0 (0.0%)
Significance (P) (Fishers exact test)		0.043		0.124		NS	0.023

one unifocal couplet during the run.

The same pattern, although not statistically significant was manifest between groups with respect to the category of fusion beats. Again, 55-65 year old runners demonstrated a higher frequency of fusion beats, 27.3% having 6 or more during testing and recovery versus 0% of the 20-30 year old runners having 6 or greater fusion beats. All 10 (100%) of the younger group experienced 0-5 fusion beats while 8 of the 11 older men (72.7%) experienced 0-5 fusion beats. No ventricular tachycardia was noted in either group.

The occurrence of ST segment depression (>1mm) was significantly greater (P=0.023) in the older men, with 45.5% experiencing some ST depression during testing and recovery as compared to 0% of the younger men experiencing any ST depression.

It is difficult to compare ventricular ectopy found here to age-matched controls due to 1) lack of standard reporting of arrythmias, 2) scarcity in the literature on ectopy in older runners (≥55 yo) during endurance exercise and 3) difference in ECG lead usage and monitoring procedures.

Only 11 of the 12 older runners were included in the above tallies due to machinery failure and forfeiture of complete ECG tracings.

3. *Plasma Catecholamines*

Figure 1 presents plasma norepinephrine concentrations at rest and during 10 KM treadmill testing. No significant differences were noted between groups at baseline, midpoint or the endpoint of the run. The endpoint value comes closest to approximating significance (P=0.06) of all values compared. Figure 2 demonstrates NE levels during recovery, and again no significant differences were noted between groups. Although at rest, older runners had higher basal NE levels, during the test and in recovery, younger runners demonstrated higher NE levels versus older runners at each sampling point. In both groups, NE values rose from baseline to peak at one minute into recovery (R-1), after which NE values progressively declined in both groups.

Plasma epinephrine levels are presented in Figures 3 and 4. No significant differences in plasma EPI were noted at rest, during 10 KM testing or in recovery between groups. The older runners demonstrated higher EPI levels at all sampling timepoints when compared to younger runners. Both groups demonstrated rising EPI levels from baseline to peak at endpoint (EP), after which EPI levels progressively declined in both groups until R-5. EPI values in both groups were slightly higher at R-10 vs. R-5.

Figure 5 compares plasma NE and EPI values between

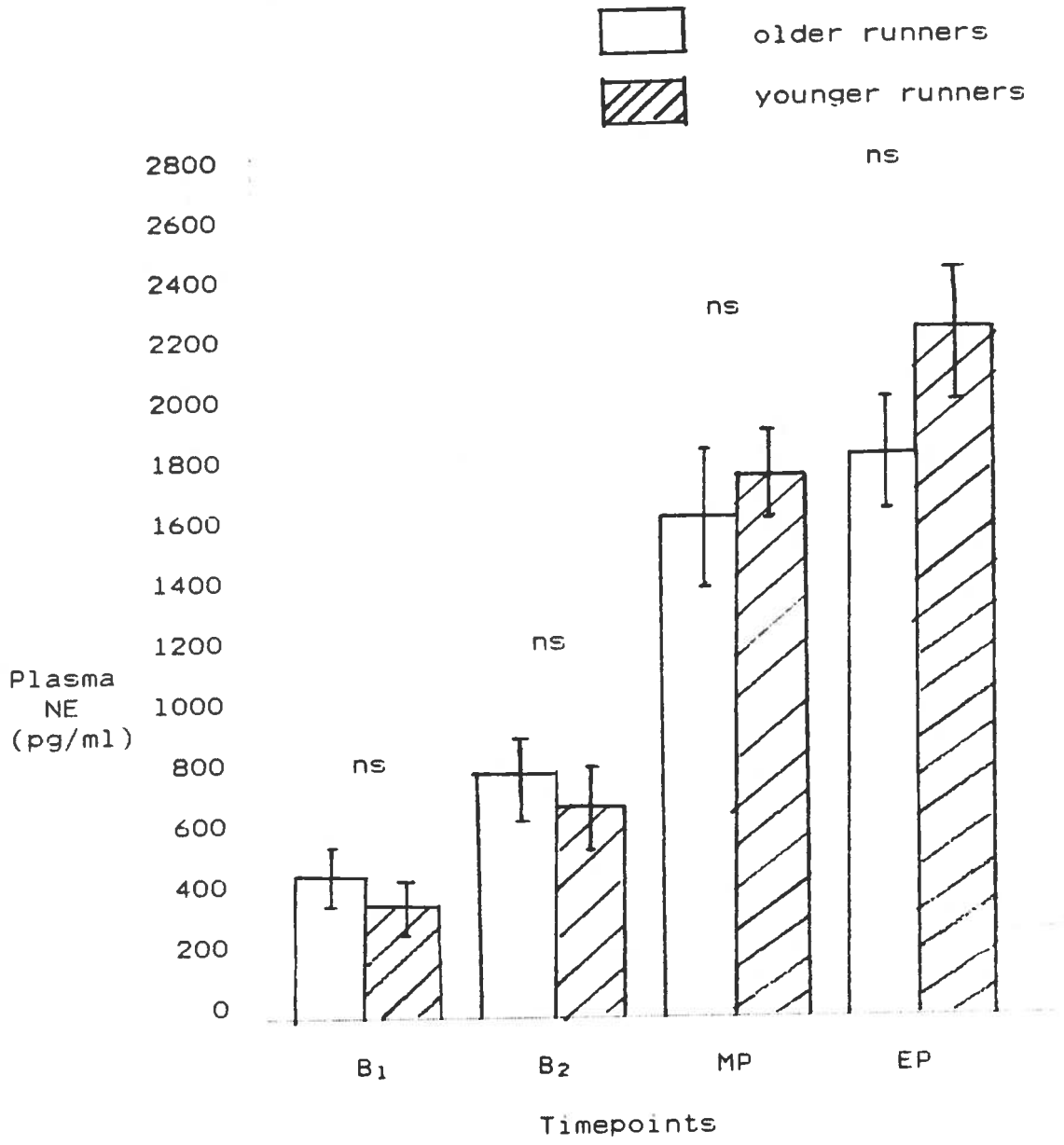

Figure 1. Plasma Norepinephrine concentrations at rest and during 10 KM treadmill testing for older and younger runners. Timepoints designated as: B_1-baseline, supine; B_2-baseline, standing; MP-midpoint; EP-endpoint. Mean values ± SE.

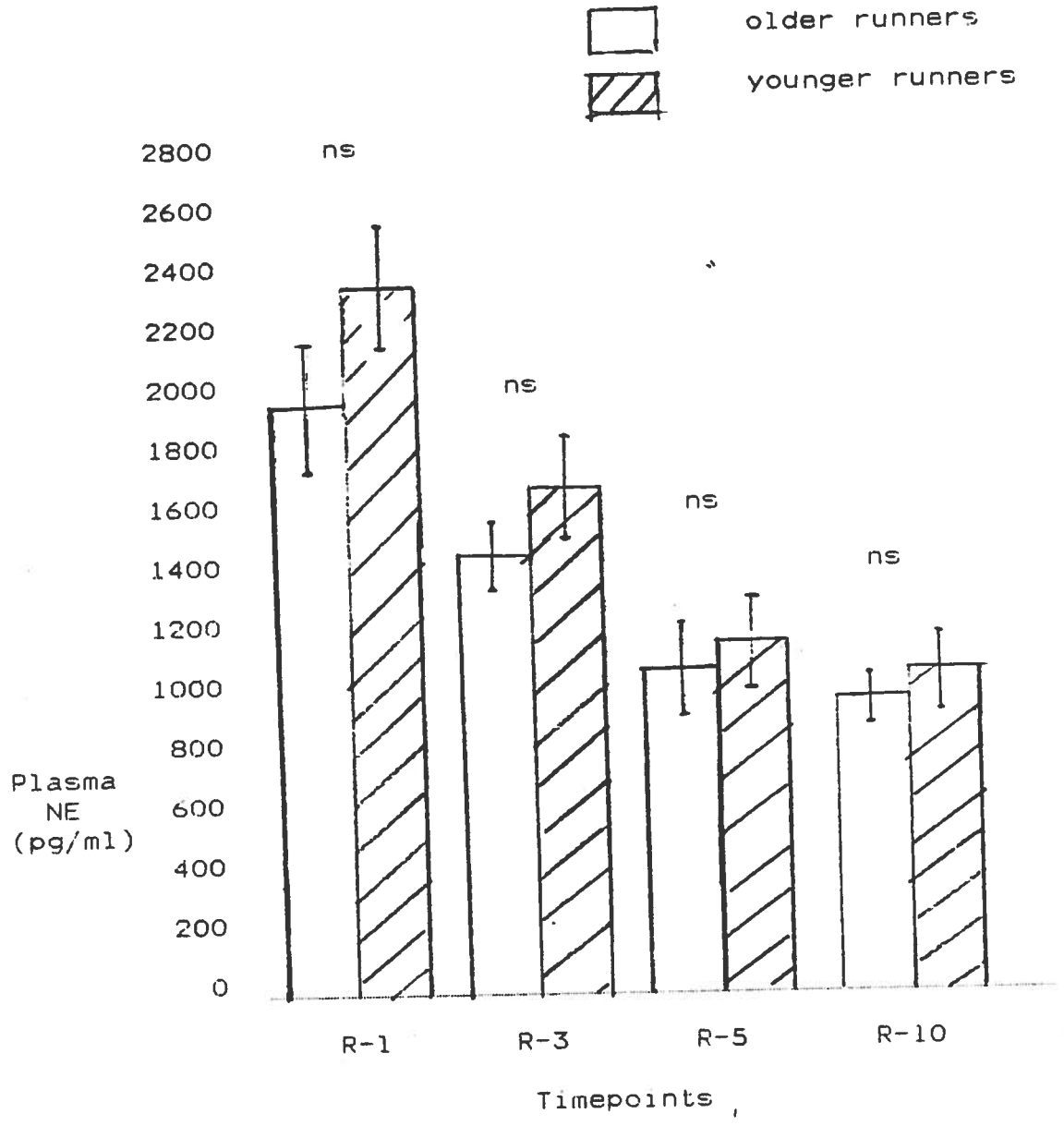

Figure 2. Plasma Norepinephrine concentrations during recovery from 10 KM treadmill testing for older and younger runners. Timepoints designated as: R-1=recovery at 1 min. post test, R-3=recovery at 3 min. post test, R-5=recovery at 5 min. post test, R-10=recovery at 10 min. post test. Mean values ± SE.

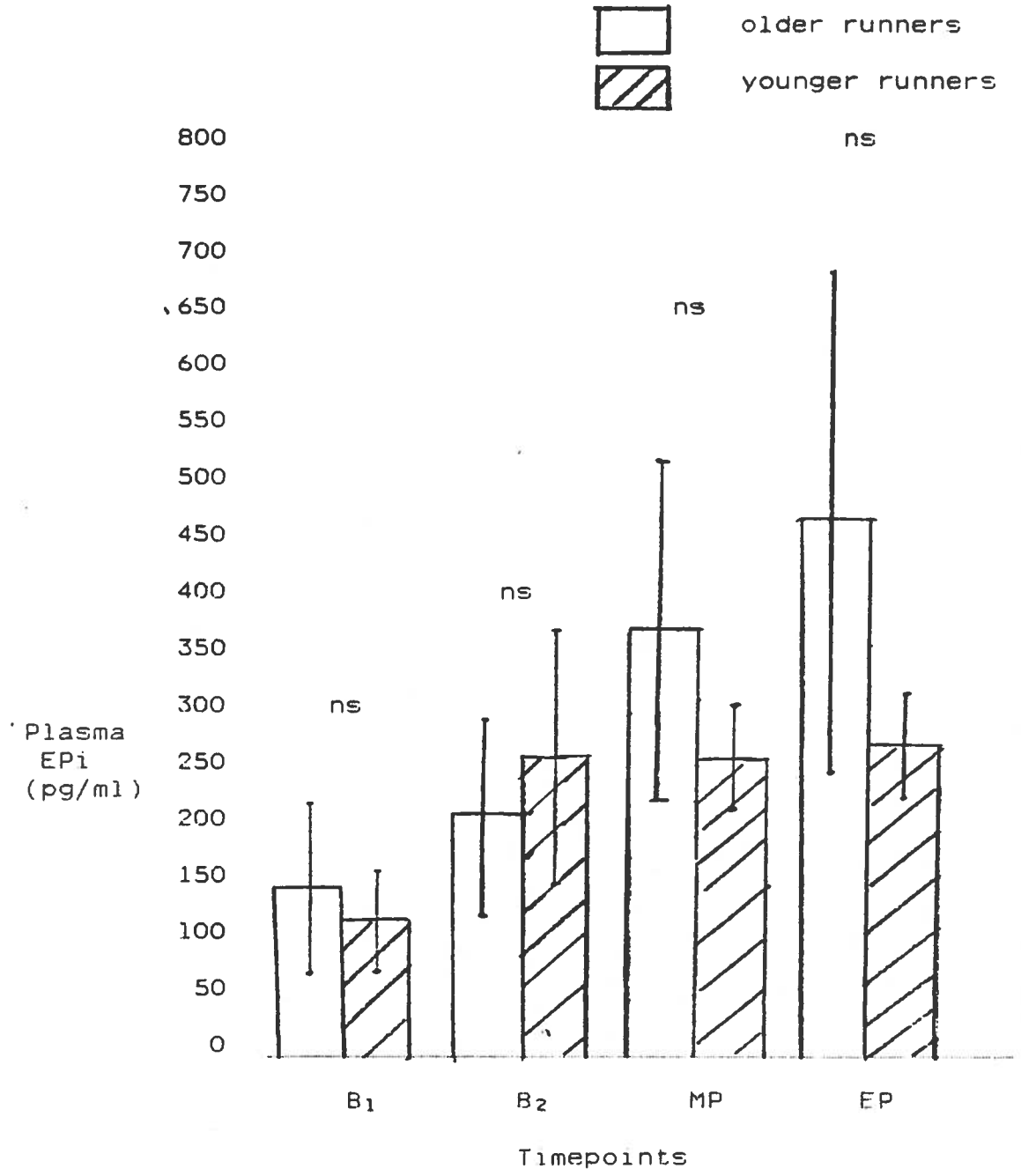

Figure 3. Plasma Epinephrine concentrations at rest and during 10 KM treadmill testing for older and younger runners. Timepoints designated as: B_1-baseline, supine; B_2-baseline, standing; MP-midpoint; EP-endpoint. Mean values ± SE.

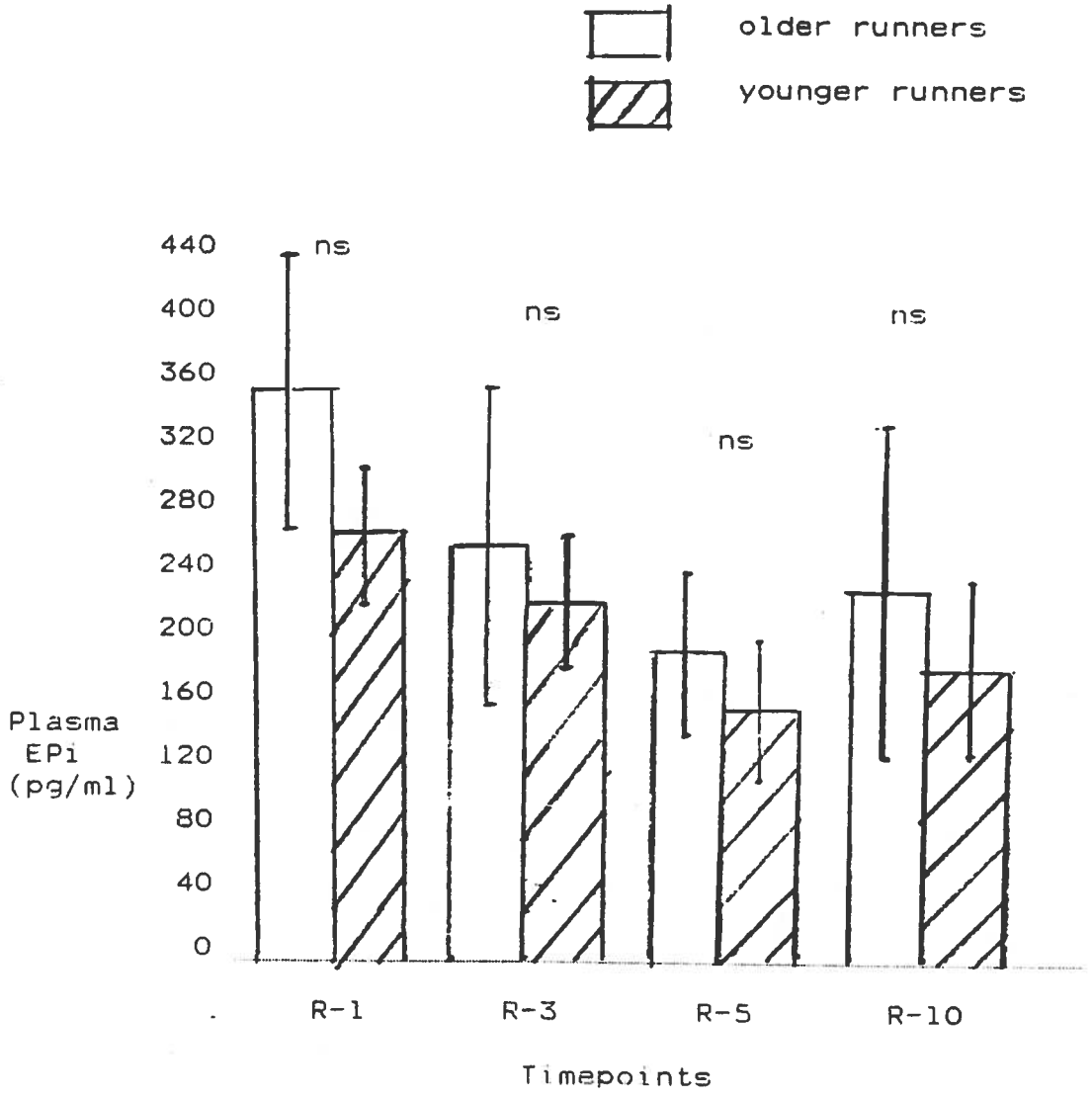

Figure 4. Plasma Epinephrine concentrations during recovery from 10 KM treadmill testing for older and younger runners. Timepoints designated as: R-1 = recovery at 1 min. post test, R-3 = recovery at 3 min. post test, R-5 = recovery at 5 min. post test, R-10 = recovery at 10 min. post test. Mean values ± SE.

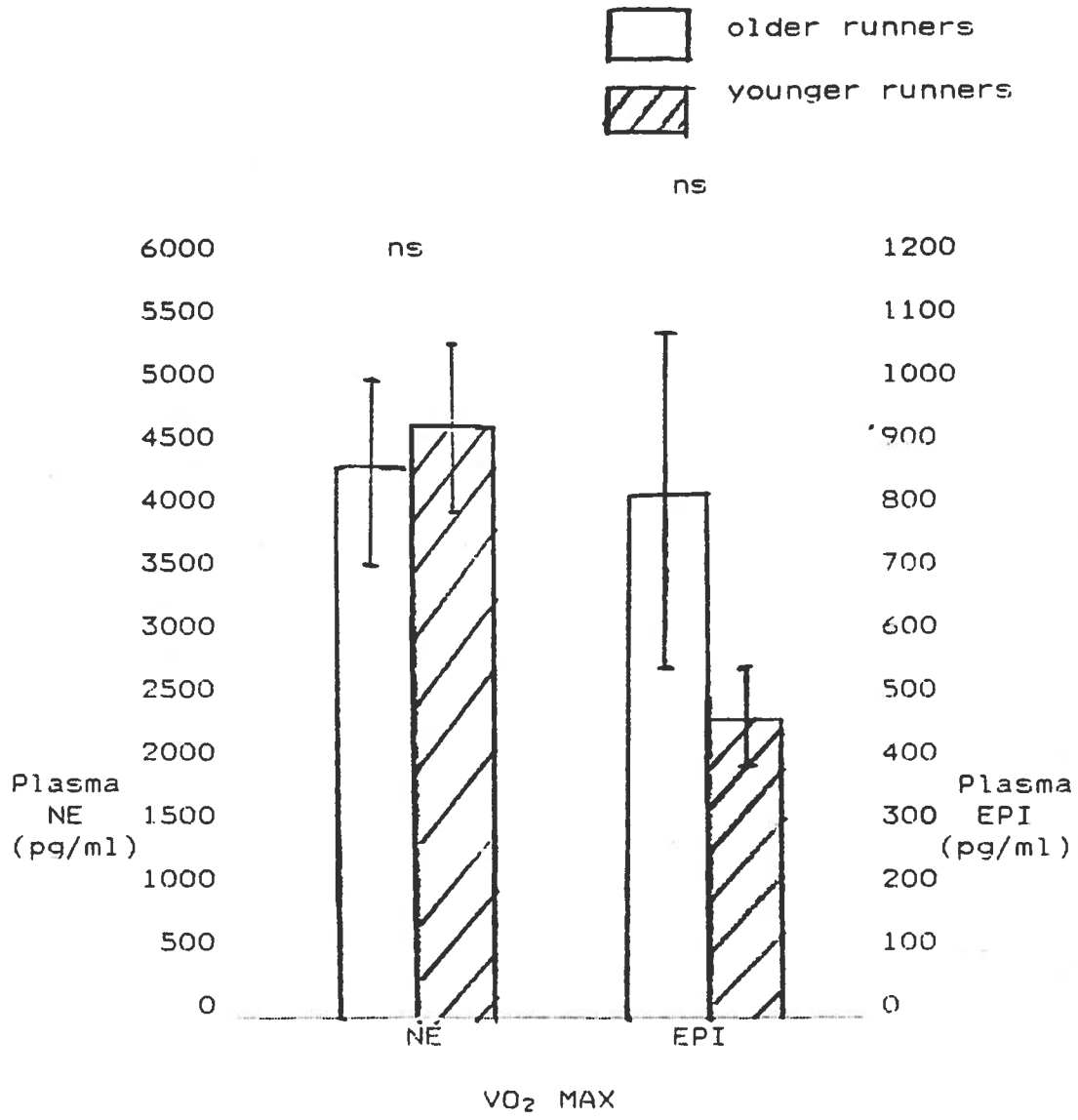

Figure 5. Plasma Norepinephrine and Epinephrine Concentrations at VO_2 max for older and younger runners. Mean values ± SE.

older and younger groups at maximal effort during VO_2 max testing. Again, plasma NE appears higher in the younger men when compared to the older men (4670.2 ± 1762.6 vs. 4337 ± 2118.2 pg/ml respectively), while EPI demonstrates the reverse; 847.2 ± 759.6 in the older men vs. 439.2 ± 163.4 pg/ml in the younger men. Neither difference was significant. These max catecholamine values were approximately twice the peak catecholamine values noted for each group during 10 KM testing.

DISCUSSION

1. *Descriptive characteristics*

The older and younger runners were comparable in terms of height, weight, BMI, resting heart rate and training level (miles run/week). The two groups were different, as expected from recruitment goals, with respect to age and 10 KM PR times. VO_2 max and maximal heart rates were also significantly higher in the direction expected (30,31), in the younger runners vs. the older runners. These four differences reached a significance level of $P \leq 0.001$.

Although the older men ran 10 KM in longer absolute times (51 minutes), as recruited to do, vs. the younger runners (40 minutes), each group ran the 10 KM at approximately 85% of their VO_2 max, giving a comparable relative effort. Thus, although not on an absolute basis but a relative one, these groups were matched and represent above average runners in each group.

2. *Frequency of ventricular arrhythmias*

The findings reported in the present study concur with those reported in the literature (3,16) regarding increased frequency of ventricular ectopy with age.

The majority of older runners experienced frequent ($\geq$6) PVC's, while only 1 of the younger runners experienced >6 PVC's, during the 10 KM run. PVC's were predominantly unifocal in both groups with the exception of one older runner who had 25 multifocal singular PVC's and 2 multifocal couplets during the run in addition to 17 unifocal singular premature ventricular beats.

Fusion beats were also counted as abnormal, and represent premature firing from ectopic sites within the ventricles which rise to fuse with normal sinus atrial conduction. Although not significant, fusion beats occurred in greater frequency in the older group. Ventricular tachycardia (VT) was not noted in either group, nor did any subject complain of dyspnea, angina or syncope during the 10 KM run.

ST segment depression ($\geq$1mm 80 ms after the J point) was noted to be significantly higher ($P \leq 0.05$) in older runners as compared to younger runners who displayed no ST depression. ST depression indicates myocardial ischemia which has been described as one of the initial events signaling catecholamine release, which in turn may set up the situation of abnormal electrical conduction patterns, e.g. PVC's, VT and ultimately ventricular fibrillation, the terminal event most commonly found in SD (15).

Thus the finding of ST depression is consistent with that of frequent PVC's and fusion beats as was seen among the older runners, and may be indicative of the predisposing situation leading to sudden cardiac death in runners. This finding in conjunction with the lack of ST depression and minimal ventricular ectopy in the younger group would therefore be consistent with reports of increasing sudden death with age (4), the younger group lacking the inciting events. Only 2 of the 11 older athletes vs. 6 of the 10 younger athletes were free of any conduction abnormalities. This difference was not deemed statistically significant (P=0.063).

Furthermore, if indeed treadmill testing underestimates abnormal cardiac electrophysiology (17) when compared to Holter-monitored outdoor running in the same individuals, treadmill ECG findings may be an inaccurate reflection of relative risk of SD occurring while a runner is performing high intensity exercise on the road.

3. *Plasma catecholamines*

The progressive plasma catecholamine rise (figure 1) during 10 KM of running seen within each group concurs with reports in the literature (32,33) of incremental increases in NE and EPI with *duration of exercise*. Futhermore, plasma NE values in both groups

continued to increase post-exercise, peaking at 1 minute into recovery, as was reported by Hagberg (21), declining during the next 10 minutes of recovery. Plasma EPI, contrarily, peaked at the endpoint of the 10 kilometers in both groups, and progressively decreased in recovery until minute 10 when a slight elevation in each age group occurred. The reason for this elevation remains unknown.

Plasma NE and EPI values within each group also were found to rise with *intensity of exercise.* Each group of runners in this study covered a distance of 10 kilometers at a relative workload of 85% of their respective VO_2 max. Plasma catecholamines measured at this workload in each group were respectively lower than the plasma catecholamines measured at 100% of VO_2 max, confirming commonly reported (18,21) results of increasing NE and EPI levels with increasing intensity of exercise.

NE and EPI in the older runners at the endpoint of the 10 KM run represent 42 and 56% of the NE and EPI levels measured at maximal aerobic capacity. NE and EPI in the younger runners similarly represent 48 and 63% of maximal catecholamine measurements. As reported by Kraemer (20) in 19-30 year old men, the slope of plasma NE and EPI rise was steepest from 83% to 100% of VO_2 max. At a workload of 83% of maximal aerobic capacity, EPI values reflected 45% of those measured at

100% of VO_2 max in Kraemer's subjects.

The magnitude of rise within each age group in both NE and EPI found in this study during both 10 KM and VO_2 max testing falls well within the range reported in the literature of catecholamine rise with both intensity and duration of exercise; NE rising incrementally greater than EPI in this and other reported studies (13,19,32).

Plasma NE and EPI values measured at baseline (supine) were found to be nonsignificantly higher in *older runners vs. younger runners*, concurring with the significant finding of Hoeldtke and numerous other reports of higher basal catecholamines in an elderly healthy population (13,22,23).

As previously mentioned in this text, a relative scarcity exists in the literature on catecholamine response in older men to endurance exercise. The most well-known study was that conducted by Palmer (23), who demonstrated *absolute* NE and EPI values to be higher in an older group of men and women (52.9 ± 0.8 years) than a younger group (13.7 ± 0.9 years) in response to 5 minutes of isometric exercise. The *relative* rise in NE however, was slightly greater among the younger group (2.4-fold increase over baseline) when compared to the older group (2.1-fold increase over baseline).

Consistent with Palmer's findings, the present study demonstrates absolute EPI values during the 10 KM

run and in recovery, to be higher in the older group vs. the younger group. Contrary to Palmer's findings, absolute NE values during the 10 KM run and in recovery were found to be lower in the older runners vs. the younger runners. Neither of these findings were deemed significant at a $P \leq 0.05$ level, however, the NE endpoint differences between groups approximated significance with $P=0.06$.

The relative rise in NE values, from supine resting levels to endpoint during the 10 KM run, were higher in the younger (8-fold increase) vs. the older runners (4.3-fold increase), again consistent with the trend seen in Palmer's subjects.

The maximal NE levels noted in this study at VO_2 max and at R-1 following the 10 KM run in both age groups superseded values reported post-MI by 2-4 fold (24), which may not reflect pre-MI values, but could none-the-less implicate dangerously high NE levels in exercisers (both young and old), which perhaps without underlying coronary pathology is inconsequential.

The *lack of significantly elevated catecholamines* in older vs. younger runners in response to a vigorous exercise bout, as initially hypothesized, may be explained by small sample size, obscuring any real differences. A larger sample size in each group might illustrate significance for smaller differences between groups. Other possible explanations include

methodological limitations of HPLC measurements, a relatively new technology in our lab. In addition, 5 subjects (3 older, 2 younger) had failing catheters during the 10 KM run, necessitating abandonment of the catheter with subsequent blood draws via a butterfly inserted immediately upon cessation of the run in a supine position. Recovery of these 5 men continued in a supine position vs. the normative recovery walking protocol. NE and EPI values of these 5 men were within two standard deviations of the mean.

Yet another explanation would involve the absence of other stressors encountered in a road racing situation experienced in potentially greater magnitude by an older competitive population. The groups also were relatively matched rather than absolutely. Perhaps a difference would have been noted between older and younger runners covering the same distance in the same time. This would however represent a very elite older group of runners and an average younger group.

In *conclusion*, this study demonstrates a significantly greater occurrence of ventricular arrhythmias and ST segment depression in older runners, implicating potentially increased cardiac risk in this group during endurance activity. This study also demonstrates that the catecholamine response to

endurace high intensity (85% VO_2 max) exercise is effort-dependent for both norephinephrine and epinephrine in both older and younger runners. The absolute and relative values noted for each parameter are consistent with those reported in the literature. Further, it was noted that plasma NE and EPI levels were not significantly different between age groups at any timepoint measured with respect to the 10 KM run or to the VO_2 max test.

Preliminary analysis reveals the ventricular ectopy and ST segment depression occurred in approximately equal frequency over the 10 KM distance in both older and younger runners. The older runners did display a non-statistically significant increase in both ventricular arrhythmias and ST depression approaching the 10 KM endpoint, when plasma catecholamine levels were approaching highest levels; the younger runners did not demonstrate this trend.

It is this basic pattern of hypoxia stimulating catecholamines which alter normal cardiac rhythm and set up a condition of electrical instability and potential ventricular fibrillation, which is hypothesized to occur in sudden cardiac death.

These changes have occurred in *moderation* in this study in healthy older men without other known cardiac risk factors. Older runners were found to have 1 mm ST segment depression, frequent unifocal PVC's and

moderately elevated (approximately 42% (NE) amd 56% (EPI) of maximal) plasma catecholamines, representing baseline values of the possible fatal changes needed to occur in SD.

In the majority of sudden death cases, *severe* underlying coronary disease with concommitant ischemia is known to exist. This condition in conjunction with 1) high intensity physical exertion, placing greater demands on the heart, aggravating ischemia and 2) other potential risk factors, may trigger critically high levels of catecholamines, prompting more lethal arrhythmias, ie. multifocal PVC's with short coupling intervals, accelerated idioventricular rhythms and ventricular tachycardia leading to ventricular fibrillation and sudden cardiac death. The actual instantaneous timing of these events may represent the master switch controlling the sudden death event; occuring at a precise lethal time in the electrical conduction circuit. In the absence of coronary atherosclerosis with concommitant ischemia, the high levels of catecholamines noted to occur at maximal effort may be of little consequence.

If the above assumption is correct, preventive strategies aimed at sudden death would involve thorough cardiac screening with a composite multivariate risk factor evaluation which includes assessment of ventricular ectopy. There is no doubt that this level

of screening remains very expensive. Further research into sympathoadrenal activity imposed on the myocardium, and elicited by afferent impulses in various conditions of tissue oxygenation, and other unexplored metabolite levels such as plasma glucose, free fatty acids and electrolytes during exercise, would continue to elucidate the role of catecholamines in sudden cardiac death.

SUMMARY

Twelve older male runners, 55-65 years old, and ten younger male runners, 20-30 years old, were studied in a cross-sectional design in an attempt to define 1) frequency of ventricular arrhythmias and 2) plasma catecholamine levels in response to a vigorous exercise bout that simulated practiced exercise regimens.

Ventricular arrhythmias and ST segment depression occurred with significantly greater frequency in older versus younger runners during the 10 KM treadmill run ($P<0.05$).

No significant differences between age groups were found for either *plasma norepinephrine or epinephrine* at rest, during the 10 KM run or in recovery.

These results potentially confer increased risk of sudden cardiac death by findings of increased ventricular ectopy in older runners, while plasma catecholamine levels appear to play no differential role in older versus younger healthy male runners in response to vigorous exercise.

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APPENDIX A: Recruitment flyer

THE
STANFORD CENTER FOR RESEARCH
IN DISEASE PREVENTION

PETER D. WOOD, PRINCIPAL INVESTIGATOR

IS DOING A

STUDY ON 10K RUNNERS

WANTED: MEN 20 - 30 YEARS OLD AND 55 - 65 YEARS OLD

WHO ARE: HEALTHY
NONSMOKER
FREE OF KNOWN CARDIOVASCULAR DISEASE OR OTHER MAJOR ILLNESS

RUN: GREATER THAN 2 10K/YEAR
10K'S BETWEEN 35-41 MIN FOR THE 20-30 YEAR OLDS
10K'S BETWEEN 45-51 MIN FOR THE 55-65 YEAR OLDS
GREATER THAN 20 MILES/WK

RECEIVE: FREE CHOLESTEROL, BLOOD PRESSURE, ELECTROCARDIOGRAM AND AEROBIC CAPACITY (VO2 MAX) MEASUREMENTS.

IF INTERESTED IN PARTICIPATING IN A SUMMER RESEARCH PROJECT COMPARING PHYSIOLOGICAL RESPONSES TO EXERCISE BETWEEN OLDER VS. YOUNGER RUNNERS

CONTACT SUSAN OR WALTER (415) 725-5311

MONDAY-FRIDAY 9AM-NOON

APPENDIX B: Newspaper Recruitment Article

Research involves serious runners

Serious runners are being sought by Stanford Medical Center researchers for a study of the physiological mechanisms that may cause abnormal cardiac rhythms among joggers and runners.

Although several studies have documented the health benefits of exercise, the dangers of sudden death during exercise also have been widely publicized—most notably by the death of author/runner James Fixx.

The intent of the study, according to Susan Garay of the Stanford Center for Research in Disease Prevention (SCRDP), is to measure physiological differences in runners by age groups to see if there are signals that might warn of cardiac problems during vigorous exercise.

Male runners are needed in two age groups, one 20 to 30 and the other 55 to 65. All volunteers must run at least 20 miles a week and have participated in at least two 10-kilometer races in the last year. The 20-30 year olds must have a 10-kilometer time of 35-41 minutes; the 55-65 year olds must have a 10-kilometer time of 45-51 minutes. The runners also must be healthy, non-smokers and free of known cardiovascular disease.

Drs. Peter Wood and William Haskell are the principal investigators on the research, which is a project of the SCRDP.

Volunteers will be given two treadmill tests at different times: one will be a test of maximum oxygen consumption or aerobic capacity and the other will be a simulated 10-kilometer run.

Blood pressure, cardiac rhythm and serum free fatty acid levels will be measured during and after the tests. In particular, volunteers will be tested for levels of catecholamines, chemicals released into the blood stream by the nervous system that influence heart function.

Catecholamine levels are known to increase with age and intensity of exercise. However, little is known about the effect of vigorous exercise on catecholamines in older men.

A second objective of the study is to determine whether vigorous exercise is associated with cardiac arrhythmias at significantly higher rates in older runners than in younger runners. Since the prevalence of heart disease increases with age, older runners may be at greater risk of cardiac abnormalities while running than younger runners. However, this is another area lacking specific data.

In addition, the study will attempt to determine the correlation between levels of free fatty acids and exercise. Research with animals has shown a relationship between excess levels of free fatty acids and heart irregularities.

All participants will receive free cholesterol, aerobic capacity, electrocardiogram and blood pressure information.

Male runners in the targeted age groups who are interested in participating in the study should call (415) 725-5311, from 9 a.m. to noon, Monday through Friday.

APPENDIX C: Telephone Interview Form

Day/Date_____

Interviewer_____

TELEPHONE INTERVIEW QUESTIONS

1. AGE/SEX: Are you between 20-30 years or 55-65 years old? Age_____

2. AVAILABILITY: Will you be in the area for next 3 months without major travel? _____Y_____N

3. RUNNING ?'s: Have you run 2 10K's in the last year? _____Y_____N

   If yes, what was the average of those 2 race times?

   _____ ((Exclusion 20-30: 35-41 min
   55-65: 45-51 min))

   How many miles/week do you run? _____ ((Excl<20mi/wk

   Do you do any other PA regularly? ___Y____N

   What & How Often?_____

4. WEIGHT/HEIGHT: What is your height? _____

   What is your weight?_____((re to wt excl. list))

5. HEALTH: Are you under an MD's care for any major medical problem?

   _____Any meds?_____

6. ORTHOPEDIC: Do you have any physical limitations which would restrict you from running? _____Y_____N

   _____

7. SMOKING: Are you currently smoking? _____Y_____N

   If yes, what do you smoke?_____((excl: smokes)

NAME:_____(Mr or Dr?)

MAILING ADDRESS_____

_____

TELEPHONE: W_____ H_____

CATEGORY: 1) Accept to next step _____ 2) Unsure/ Recontact _____ 3) Reject (circle reason why) _____

If accept, schedule for ORIENTATION SESSION (with spouse if so desired) at which Dr.Peter Wood (P.I.) and assistants will discuss research project and requirements. Meeting will be held at WRCR in the eve.

APPENDIX D: Mailing Information Form

Mailing Information - 10KM STUDY

Please print clearly in boxes provided. ID: [ ][ ][ ] (1-3) [A] (4)

NAME:

Title [ ][ ][ ][ ] (5-8)

First [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (9-18)

Middle [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (19-28)

Last [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (29-42)

LIVING PARTNER'S NAME:

First [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (43-52)

Middle [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (53-62)

Last [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (63-76)

HOME ADDRESS:

Number & Street [ ] (77-100)

City [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (101-116)

ZIP [ ][ ][ ][ ][ ] (117-121)

WORK ADDRESS:

(Dup col 1-4)

Stanford Department (I.D. Mail) or Company Name [ ] (5-30)

Company Address [ ] (31-55)

Company City [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (56-71)

ZIP [ ][ ][ ][ ][ ] (72-76)

PHONES:

Home ([ ][ ][ ]) [ ][ ][ ] - [ ][ ][ ][ ] (77-86)

Work ([ ][ ][ ]) [ ][ ][ ] - [ ][ ][ ][ ] (87-96)

Extension [ ][ ][ ][ ] (97-100)

Prefer mail to: Work [ ] 1 (101) Home [ ] 2

Prefer calls to: Work [ ] 1 (102) Home [ ] 2

In case of Emergency call:

Name: _____

Address: _____

Phone: _____

Name of personal physician: _____

Address: _____

Phone: _____

If you would like the results of your Baseline Measurements sent to the above Physician, please check:

YES [ ] 1 (103)

NO [ ] 2

APPENDIX E: Demographic Data Form

DEMOGRAPHIC DATA QUESTIONNAIRE 10KM STUDY

	ID#	VISIT#	FORM	DATE
STAFF USE ONLY	☐☐☐	☐☐	☐	☐☐/☐☐/☐☐
	(1-3)	(4-5)	(6)	(7-12)

Please print full name:_____

(13-20) 1. Age: ☐☐ 2) Birthdate: ☐☐/☐☐/☐☐

3. Ethnic Background (Check appropriate box):

(21)
- ☐ 1. Caucasian
- ☐ 2. Black
- ☐ 3. Asian
- ☐ 4. American Indian
- ☐ 5. Hispanic/Latino
- ☐ 6. Other

4. Years of education:
(e.g. High School Grad = 12, College Grad = 16, etc.)

(22-23) ☐☐

5. Outside Interests/Hobbies:_____

_____

6. Occupation Profile

Current Job Title _____

Number of years in this position:

(24-25) ☐☐

7. Marital Status

(26)
- ☐ 1. Never Married
- ☐ 2. Married
- ☐ 3. Separated
- ☐ 4. Divorced
- ☐ 5. Widowed

Name of Wife or Living Partner_____

8. How many miles do you live from the Stanford Campus? _____

(27-28) ☐☐

9. If you don't work at Stanford, how many miles from Stanford is your workplace?

(29-30) ☐☐

APPENDIX F: Physical Activity Form

10K Study

Physical Activity Questionnaire

1. How many years have you been running 10K races? _____ years

2. How many miles per week do you run in training? _____ mpw

3. What is your average pace on a training run? _____ min/mile

4.(a) Do you run interval/anaerobic workouts? Y N

(b) If yes, how often and how long?

5. What is your longest training run in preparation for a 10K? _____ miles

6. How many days per week do you train? _____ dpw

7. What is your best 10K time? ____ min ___ sec

8. At what age did you run your best 10K time? _____

9. What do you do immediately following a 10K race? (e.g. walk, sit, jog, stand)

10. Have you run a marathon? If yes, how many and what is your best time? Y N

11. Do you cross-train? (e.g. swimming, cycling, weight-lifting) If yes, how often and how much? Y N

12. Do you engage in any other rigorous physical activity? If yes, how often and how much? Y N

13. Have you smoked in the past? If yes, how long and how much? Y N

14. Do you drink alcohol? If yes, what type and how much? Y N

15. Do you alter your diet in any way? (e.g. vegetarian, low fat-high carbohydrate) If yes, please explain Y N

P.A. Questionnaire(continued)

16. Do you drink coffee? If yes, how much? Y N

17. Do you carbohydrate-load before a 10K race? If yes, please explain Y N

18. Do you eat the morning of a 10K race? If yes, please explain Y N

APPENDIX G: Medical History Form

MEDICAL HISTORY QUESTIONNAIRE 10K STUDY

PARTICIPANT QUESTIONNAIRE

PARTICIPANT'S NAME _____ BIRTHDATE _____

HEIGHT ___ft.___in. WEIGHT _____lbs. TODAY'S DATE _____

FAMILY HISTORY

Please check where appropriate:

	Father	Mother	Brother				Sister				Children					
			1	2	3	4	1	2	3	4	1	2	3	4	5	6
Diabetes																
Heart Trouble																
High Blood Pressure																
Stroke																
Asthma, Hives, Hayfever																

Please indicate ages of relatives listed above who are living _____

_____

If any of your relatives listed above has died, please indicate the relation to you, cause of death, and age at death.

_____

_____

_____

INSTRUCTIONS: Put a check in those boxes applicable to you and in the "yes" or "no" space. If lines are provided write in your answer.

PERSONAL HISTORY

Have you ever had ...

YES	NO	
___	___	Scarlet Fever
___	___	Rheumatic Fever
___	___	Diphtheria
___	___	Arthritis, Rheumatism
___	___	Other Bone, Joint Problems
___	___	Neuritis, Neuralgia
___	___	Bursitis, Sciatica, Lumbago
___	___	Any Eye Disease, Injury, Impaired Sight
___	___	Any Ear Disease, Injury, Impaired Hearing
___	___	Any Trouble with Nose, Sinuses, Mouth, Throat
___	___	Convulsions
___	___	Paralysis
___	___	Loss of Consciousness
___	___	Headaches: Frequent or Severe
___	___	Thyroid: Overactive, Underactive, or Enlarged
___	___	Abnormal Thirst
___	___	Diabetes

 NAME _____

Have you ever had ...

YES	NO	
___	___	Skin Disease
___	___	Cough: Frequent or Chronic
___	___	Chronic Lung Disease or Asthma
___	___	Pneumonia
___	___	Heart Disease
___	___	High Blood Pressure
___	___	Unusual Shortness of Breath with Exertion or at Night
___	___	Swelling of Hands, Feet or Ankles
___	___	Varicose Veins
___	___	Kidney Disease, or Stones
___	___	Bladder Disease
___	___	Blood in Urine
___	___	Albumin, Sugar, Pus, etc., in Urine
___	___	Prostate Trouble
___	___	Stomach Trouble or Ulcers
___	___	Appendicitis
___	___	Gall Bladder Disease
___	___	Other Bowel Disease
___	___	Jaundice, Hepatitis or Liver Disease
___	___	Cancer
___	___	Any Other Disease, Specify _____
		_____

WEIGHT: (lbs.) Now _____ One Year Ago _____ Maximum _____ When _____

ALLERGIES

Are you allergic to ...

YES	NO	
___	___	Any Drugs, Specify _____
		_____
		_____
___	___	Adhesive Tape
___	___	Any Foods

SURGERY

Have you ...

YES	NO	
___	___	Had Any Operations
___	___	Been Hospitalizated for any Illness, Specify _____
		_____
		_____

NAME _____

HABITS

Do You ...

YES	NO		
___	___	Exercise Regularly	
___	___	Sleep Well	
___	___	Recreation: Do you participate in sports or have hobbies which give you relaxation at least 3 hours a week?	

Do You Use ...

NEVER	OCCASIONALLY	FREQUENTLY	DAILY	
_____	_____	_____	_____	Laxatives
_____	_____	_____	_____	Vitamins
_____	_____	_____	_____	Sedatives
_____	_____	_____	_____	Tranquilizers
_____	_____	_____	_____	Sleeping Pills, etc.
_____	_____	_____	_____	Aspirin, etc.
_____	_____	_____	_____	Cortisone
_____	_____	_____	_____	Alcoholic Beverages
_____	_____	_____	_____	Appetite Depressants
_____	_____	_____	_____	Recreational Drugs

MEDICATIONS

	Name	Amount	Date Started
Thyroid Medication			
Insulin Shots			
Tablets for Diabetes			
Hormone Shots			
Other Medications			

APPENDIX H: Medical Research Subject's
Bill of Rights and Consent Form

STANFORD CENTER FOR

RESEARCH IN DISEASE PREVENTION

INFORMED CONSENT FOR RESEARCH STUDY ON PHYSIOLOGIC RESPONSES TO VIGOROUS EXERCISE IN MEN

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Persons who participate in a medical experiment are entitled to certain rights. These rights include but are not limited to the subject's right to: be informed of the nature and purpose of the experiment; be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized; be given a description of any attendant discomforts and risks reasonably to be expected; be given an explanation of any benefits to the subject reasonably to be expected, if applicable; be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits; be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise; be given an opportunity to ask any questions concerning the experiment of the procedures involved; be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice; be given a copy of the signed and dated consent form; and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

INFORMED CONSENT

You are invited to participate in a cross-sectional research study which will investigate and compare physiological responses to vigorous exercise between older and younger men who are regular runners. Participants will be healthy nonsmokers aged either 20-30 or 60-70. We will study your:

(1) plasma catecholamine response (adrenalin, noradrenalin) to a bout of vigorous exercise;

(2) serum free fatty acid response to a bout of vigorous exercise;

(3) blood pressure, heart rate and cardiac rhythm response to a bout of vigorous exercise;

(4) baseline lipid and lipoprotein levels.

These measurements will provide us with information on potential markers for heart problems during and immediately post-exercise. If you decide to participate, we first need to screen for elevated triglycerides, cholesterol or blood pressure and any history of medical problems which might interfere with interpretation of your data. You will be asked to arrive in our clinic at 730 Welch Road, after at least 12 hours of fasting, for a 20-minute visit for blood tests, height and weight, blood pressure and physical activity questionnaire. We will inform you of your results promptly. If we find no reasons for exclusion, we will ask you to schedule one additional visit, lasting approximately 2 hours, during which you will undergo a treadmill test comparable to a 10 kilometer run. During this treadmill test, and during recovery from it, we will monitor oxygen intake, blood pressure, and heart rate by electrocardiogram. The exercise test will be

performed by running the equivalent of 10 kilometers on the treadmill at a constant speed and slope. The test will be stopped if you signal that you so wish, but it may be stopped sooner if the test supervisor's observations suggest that it may be unnecessary or unwise to continue. The risks in performing such vigorous exercise include irregular, low, or very rapid heart beats, or large changes in blood pressure. These changes can seriously reduce circulation, and in very rare instances have resulted in collapse. A sample of 90 mls (about 3 ounces) of blood will be drawn for subsequent determination of catecholamines and free fatty acids. This blood will be drawn through a small plastic tube placed in a vein in your arm and taped in place. This tube will be left in your arm during the exercise test (a total of about one hour) so that we may obtain samples of blood during the test, and for the 15-minute recovery period immediately after the test.

There is little risk associated with any of the above procedures, although in extremely rare instances blood-drawing has resulted in infections and hematomas (black and blue marks).

We cannot and do not guarantee or promise that you will receive any benefits from this study. We will make any data that we collect available to you at the end of the study. Any data under the investigator's control will be disclosed in a manner that does not reveal your identity. In the interest of public safety, however, information will be provided to Federal and regulatory agencies as required. Any inquiries concerning procedures can be directed to Susan Garay, M.S., or Dr. Peter D. Wood, principal investigator, at 497-6254.

In the event of physical injury that arises solely out of the negligence of the Stanford Medical Center or its staff in this study, reimbursement for expenses incurred for necessary medical treatment and hospitalization is available. For further information, please call 497-5244 or write the Medical Center for the Protection of Human Subjects at 851 Welch Road, Room 115, Palo Alto, California, 14304. In addition, if you are not satisfied with the manner in which this study is being conducted, you may report any complaints to the same telephone number and address.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PRINCIPAL INVESTIGATOR AND STAFF AND THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED. A COPY OF THIS FORM IS AVAILABLE TO YOU UPON REQUEST.

_____ _____

Signature Witness Signature

_____ _____

Date

APPENDIX I: Clinic Screening Form

SCREENING FORM -- 10K STUDY

PARTICIPANTS NAME_____

1) FORMS COMPLETED:
- Mailing..... Y N
- Demographic..... Y N
- Medical History..... Y N
- Informed Consent..... Y N

2) At what time did you last have anything by mouth, other than water? Time_____pm

3) What is the present time? Time_____am

4) How many hours has subject fasted? _____hours

5) Have you performed any vigorous physical activity today? Y N

6)
- HEIGHT(cm)_____.__
- WEIGHT(kg)_____.__
- overwt? Y N

7)

	RANDOM ZERO	CORRECTED
BLOOD PRESSURE#1:	_____/_____	_____/_____
BLOOD PRESSURE#2:	_____/_____	_____/_____

RESTING HEART RATE: _____/min.
(count for 15 sec X 4)

BLOOD PRESSURE#3: _____/_____ _____/_____

MEAN OF BP #2 & #3 CORRECTED: _____/_____

8) FASTING BLOOD RESULTS:
- Total Cholesterol mg/dl _____
- Triglycerides mg/dl _____

9) GLYCOSURIA as indicated by urine dipstick Y N

10) Does this case need review? Y N

ACCEPT _____ HOLD_____ REJECT_____