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Previous research has demonstrated a reduction in fat utilization during a single bout of exercise following ingestion of nicotinic acid (NA). The potential to adapt to chronic NA administration has not been evaluated, although many people take large doses of NA to reduce serum cholesterol. The purpose of this study was to investigate the changes in fuel utilization, based upon the respiratory exchange ratio (RER) and pre- and post-exercise blood-borne substrates (glucose, lactate, glycerol, and free fatty acid [FFA]), during 30 min of submaximal treadmill running (SUB) at 6 mph throughout three weeks of pharmacologic doses of NA. All SUBs were at the same time in the morning, following a 12-14 hour fast and involved a pre- and post-run blood draw from an antecubital vein. Another purpose of the study was to examine the effect of three weeks of NA ingestion on total and HDL cholesterol of trained runners.

Eight experienced male runners (aged 18-41 years), with average $\dot{V}O_2$ max

values of 60.8 $\pm$ 5.5 (SD) $ml \cdot kg^{-1} \cdot min^{-1}$, performed the first SUB to establish baseline values. Two days later, the second SUB was performed one hour after the ingestion of 1 g of NA. Then 21 days of NA ingestion followed, starting with 100 mg taken 3 times/day and increased by 100 mg/day until by Day 10 the dose reached 1 g, 3 times/day, which was maintained for the remaining treatment days. The third and fourth SUBs were on Days 11 and 21, respectively. The results indicated no change in heart rate and VO_2 during the four SUBs. There was a significant change in the RER values using a repeated-measures ANOVA procedure (RER: SUB1, .871$\pm$.021; SUB2, .919$\pm$.023; SUB3, .898$\pm$.019; SUB4, .896$\pm$.023, $p < .001$). Post hoc analysis revealed SUB2, SUB3, and SUB4 were significantly higher than SUB1 and that SUB2 was also significantly higher than SUB3 and SUB4. The trend in the RER indicates that the initial NA dose significantly reduced fat utilization and that continued NA treatment resulted in a persistent, though lessened inhibition during subsequent runs. Repeated-measures ANOVA procedures were also used to compare pre- and post-submaximal run levels and delta values for glucose, glycerol, and FFA. None of the pre-run values were significantly different except for the pre-run FFA values. The post-submaximal run values were all significantly different, as were the delta values, with the exception of the delta values for glucose. Post hoc comparisons for pre, post, and delta FFA for SUB1 were significantly different from SUB2, SUB3, and SUB4. Other post hoc analyses revealed that post-run and delta glycerol values for SUB1 were significantly different from SUB2, SUB3, and SUB4. A repeated-measures ANOVA procedure indicated that there were no significant differences in the delta values for lactate levels for the submaximal runs.

The Student's t statistic was used to compare pre- and post-treatment total and HDL cholesterol. Significant decreases occurred in total cholesterol, from 195.3 to 174.5 $mg \cdot dl^{-1}$, and significant increases occurred in HDL cholesterol, from 56.2 to 63.0 $mg \cdot dl^{-1}$.

Nicotinic acid treatment caused significant decreases in fat utilization. The RER data demonstrated an incomplete adaptation to chronic ingestion of nicotinic acid over the three week period, whereas the blood-borne substrates did not indicate any lessening of the inhibition on fat mobilization. The cholesterol levels were significantly affected by nicotinic acid treatment, showing a decrease in total cholesterol and an elevation in HDL cholesterol.

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CHAPTER I

INTRODUCTION

In a normal resting state, oxygen is consumed by the various organs (GI tract, kidneys, brain, skeletal muscle) in a relatively equal distribution (Åstrand and Rodahl, 1986). But since exercise produces a considerable stress, it forces the body into the unique condition of having 90% of the oxygen consumption serve the needs of skeletal muscle alone (Issekutz, Miller, and Rodahl, 1966). Unless an individual is in a state of starvation, when protein would become a significant factor, the energy to supply the musculature during the stress imposed by exercise is derived almost exclusively from carbohydrate and fat (Åstrand and Rodahl, 1986).

It was Christensen and Hansen (1939) who discovered that along with carbohydrate utilization, fat metabolism is a factor in supplying energy to the working muscles. When it was evident that both carbohydrate and fat could serve as energy substrate, the factors that regulate substrate utilization during exercise began to be investigated. Analysis of respiratory exchange ratio (RER), the ratio of carbon dioxide production to oxygen consumption (VCO_2/VO_2), is used to indicate the relative usage of the two fuels during rest or steady state exercise (Shephard, 1982). The process of utilizing carbohydrates as a fuel source results in equal amounts of oxygen consumed and carbon dioxide produced; utilizing fats increases oxygen

consumption compared to carbon dioxide production. Thus, the greater the contribution of fats, the lower the RER value and the greater the contribution of carbohydrates, the higher the RER value (range of .70-1.00) (Brooks and Fahey, 1984).

A vitamin in the B complex, niacin or nicotinic acid, has been shown to alter substrate utilization. It is well established that nicotinic acid inhibits lipolysis in adipose tissue, which decreases plasma free fatty acid (FFA) levels (Carlson, Havel, Ekelund and Holmgren, 1963). Inhibition of triacylglycerol breakdown and stimulation of triacylglycerol synthesis, increasing the rate of FFA esterification, are the central mechanisms for the decreased fat utilization (Carlson, 1963).

Several investigators have examined the relationship between nicotinic acid and decreased fat utilization. Madsen and Malchow-Moller (1983) investigated the effects of nicotinic acid ingestion on adipose tissue blood flow in rats. Compared to controls, rats infused with nicotinic acid demonstrated significantly reduced adipose tissue blood flow (28%). Adipose tissue blood flow has proven to be an indication of the intensity of lipolysis: the higher the adipose tissue blood flow, the greater the lipolytic activity (Nielson, Bitsch, Larsen, Larsen and Quaade, 1968). Futhermore, in adipose tissue extracted from humans, Arner and Ostman (1983) demonstrated inhibited lypolysis with nicotinic acid ingestion. The nicotinic acid dose (10 μmol/L) caused a 25% inhibition of the conversion of radioactive glucose into triacylglycerol in human adipose tissue. The vitamin also decreased the rate of glycerol release by 50% and significantly reduced the tissue levels of diacylglycerols. The researchers

demonstrated that nicotinic acid inhibits both the synthesis and breakdown of triacylglycerols; however, the reduced breakdown had a more pronounced effect, thus reducing the mobilization of FFA.

In addition to these findings in a resting state, investigations have also examined the effects of nicotinic acid administration on substrate utilization during bouts of exercise. Carlson et al. (1963) infused two subjects 13 times with a total of 1.4 g of nicotinic acid throughout a rest (60 min), exercise (120 min) and rest (60 min) routine on the cycle ergometer in order to assess RER and plasma levels of FFA, glycerol, and glucose. The subjects had begun nicotinic acid ingestion 4-5 days prior to testing and had gradually increased their dose to 500 mg three times/day. It was reported that, compared to six subjects without nicotinic acid, those infused with nicotinic acid generally had higher RER values and decreased plasma FFA, glycerol, and glucose levels. The authors concluded that the most important findings were: (a) nicotinic acid decreased the rate of FFA mobilization at rest and (b) nicotinic acid inhibited the normal mobilization of FFA in exercise.

Another group of researchers, (Bergström, Hultman, Jorfeldt, Pernow and Wahren, 1969), used 15 trained subjects, who were not active in competition, to investigate the effect of 1.6 g (1 g IV and 600 mg orally) of nicotinic acid during cycle ergometer exercise of various durations and intensities. Although all subjects experienced the work as more fatiguing after nicotinic acid administration, the ability to perform the different protocols was not altered by administering nicotinic acid. Also, the RER values were significantly elevated with nicotinic acid administration

and there was a significant decrease in muscle glycogen.

The changes in substrate utilization, specifically a decrease in fat utilization with administration of nicotinic acid, appear to be well documented. Interestingly, researchers have taken advantage of nicotinic acid's effects to investigate other unrelated phenomena. Two experiments examined temperature regulation using nicotinic acid to suppress the normal rise in plasma FFA concentration during acute cold exposure (Hanson, Johnson and Engel, 1965; Martineau and Jacobs, 1989). Other investigators (Constable, Favier and Holloszy, 1986) used nicotinic acid to decrease availability of FFA and speed glycogen depletion to examine phosphorylase activation after exhausting exercise in rats.

Another related issue that has been investigated is the effect of nicotinic acid on cholesterol levels. Numerous investigators have reported changes in plasma cholesterol levels as a result of nicotinic acid treatment (Alderman et al., 1989; Atmeh, Shepherd and Packard, 1983; Blankenhorn, et al., 1987; The Coronary Drug Project Research Group, 1975; Glueck, 1985; Gurakar, Hoeg, Kostner, Papadopoulos and Brewer, 1985; Hanefeld, Hora, Schulze, Rothe, Barthel and Haller, 1984; Hoogwerf, Bantle, Kuba, Frantz and Hunninghake, 1984; Kane et al., 1981; Shepherd, Packard, Patsch, Gotto and Taunton, 1979). The effects of nicotinic acid treatment on cholesterol levels are clearly evident in the 1983 article of Hoogwerf and others. These investigators used a 3 g/day dose of nicotinic acid for 12 weeks and compared cholesterol levels to a pre-treatment 6 week baseline period. The study demonstrated that nicotinic acid treatment resulted in a significant reduction from

baseline of total cholesterol (28%) and very low density lipoprotein (VLDL) cholesterol (56%), as well as a significant increase in high density lipoprotein (HDL) cholesterol (28%) and HDL/LDL (low density lipoprotein cholesterol) ratio (62%).

An additional factor that has been implicated in altering plasma lipoprotein concentrations is habitual exercise (Farrell and Barboriak, 1980; Heath, Ehsani, Hagberg, Hinderliter and Goldberg, 1983; Hespel et al., 1988; Rotkis, Boyden, Stanforth, Pamenter and Wilmore, 1984; Wood et al., 1983). Wood et al. (1983) randomly divided 81 sedentary males into a running group and a control group to examine lipoprotein concentrations for one year. Of the 48 assigned to the running group, 25 of them averaged at least 12.9 km (8 miles) per week. These 25 males significantly ($p < .045$) increased their plasma HDL cholesterol.

It is apparent from the literature that nicotinic acid ingestion can affect substrate utilization in bouts of exercise. But no investigation has attempted to examine the adaptations in exercise substrate utilization during nicotinic acid ingestion over time. Another question that has not been examined is the effect of nicotinic acid ingestion on lipoprotein concentrations in habitual exercisers. This study, therefore, addressed both of these questions. The design of the study involved four testing times for the submaximal runs: (1) a submaximal run before the nicotinic acid treatment began (SUB1), (2) a submaximal run at Day 1 of the nicotinic acid treatment period (SUB2), (3) a submaximal run at Day 11 of the nicotinic acid treatment period (SUB3), and (4) a submaximal run at the end (Day 21) of the nicotinic acid treatment period (SUB4).

Purpose Statement

The purpose of this study was to investigate the changes in substrate utilization (using RER values) during and blood-borne substrate levels (glucose, glycerol, FFA, and lactate) before and after 30 min of submaximal (6 mph) treadmill running throughout three weeks of pharmacologic doses of nicotinic acid. Total and HDL cholesterol levels were also assessed before and after the nicotinic acid treatment period.

Delimitations and Assumptions

This study was delimited to (a) eight well-trained males between the ages of 18-41 years, (b) the cooperation of the subjects to finish the testing, and (c) the subject's adaptation to nicotinic acid administration over a three week period.

The assumptions were that the subjects would maintain their regular training programs and accurately complete the training logs.

Hypotheses

The following hypotheses were tested at the .05 level of significance.

1. Fuel utilization would shift toward greater carbohydrate metabolism at the start of nicotinic acid treatment and then adapt back to pre-nicotinic acid levels of fuel utilization. Nicotinic acid treatment would result in an increase in RER values for SUB2 followed by decreasing RER values in SUB3 and SUB4 as the subjects adapted to the nicotinic acid dose.

2. The nicotinic acid dose would cause a decrease in fat mobilization and then there would be a return to pre-treatment levels with continued nicotinic acid administration. Glycerol and FFA levels would be lower in SUB2 and then would increase in SUB3 and SUB4.
3. Circulating glucose levels would increase in line with increased carbohydrate metabolism and then decrease to normal levels with continued nicotinic acid administration. Glucose levels would be elevated in the SUB2 followed by decreasing levels in the SUB3 and SUB4.
4. The workload would require very little anaerobic metabolism so lactate levels would not change throughout the experiment.
5. Total cholesterol levels would decrease throughout the nicotinic acid treatment period.
6. Levels of HDL would increase throughout the nicotinic acid treatment period.

CHAPTER II

REVIEW OF LITERATURE

Niacin, or nicotinic acid, has been used since the early 1950s as treatment for hyperlipidemia (Altschul, Hoffer and Stephen, 1955). This chapter will begin with a review of current literature regarding metabolism of foodstuffs and lead to a discussion of the research involving niacin. Following is a review of current literature concerning the effects of exercise on cholesterol levels.

The first section pertains to metabolism and niacin. The specific topics reviewed are: (a) substrate utilization and (b) niacin. Under niacin is a discussion of the (1) sources of niacin, (2) niacin absorption and storage, (3) niacin functions, (4) nicotinic acid doses, and (5) tolerance of nicotinic acid.

Section two reviews investigations using nicotinic acid. This will include: (a) nicotinic acid effects on fuel utilization at rest, (b) nicotinic acid effects on fuel utilization during bouts of exercise, and (c) nicotinic acid effects on cholesterol levels.

The third and last section discusses the effects of exercise on cholesterol levels which is followed by a chapter summary.

Substrate Utilization

Indirect calorimetry is a technique used to determine type and rate of substrate utilization, based upon the analysis of gas exchange. The advantages of this method are that it is noninvasive, accurate, and relatively inexpensive. Indirect calorimetry, developed in the 1890s, was originally used to estimate metabolic rate from measurements of oxygen (O_2) consumption and carbon dioxide (CO_2) production. More recently, indirect calorimetry has been used to investigate substrate utilization, or fuel utilization, in a variety of exercise and nonexercise situations (Ferrannini, 1988).

Direct calorimetry, which measures total heat loss from the body, was the basis for establishing the accuracy of indirect calorimetry. Atwater and Rosa (1899) built a device capable of measuring heat production, O_2 consumption, and CO_2 production simultaneously. Thus, the relationship between direct and indirect calorimetry was established, making possible the determination of metabolic rate from O_2 consumption and CO_2 production (Brooks and Fahey, 1984).

Utilizing the established validity of indirect calorimetry, O_2 consumption can be used to estimate metabolic heat production. In a similar manner, the type of substrate being used can be determined from the ratio of CO_2 produced (VCO_2) to O_2 consumed (VO_2). The VCO_2/VO_2, respiratory exchange ratio (RER), provides information on the relative contribution of the foodstuffs being used to supply the energy needs of the body. The RER accurately assesses substrate utilization in a steady-state situation not exceeding the lactate threshold, at which point anaerobic

metabolism contributes significantly and nonrespiratory CO_2 is produced. When carbohydrate (glucose -- $C_6H_{12}O_6$) is completely oxidized to CO_2 and water (H_2O), the equation is:

$$C_6H_{12}O_6 + 6O_2 \text{ -----> } 6CO_2 + 6H_2O$$

Thus, one volume of CO_2 is produced for each volume of O_2 consumed and the RER $= 6CO_2/6O_2 = 1.00$. If free fatty acids are used exclusively as the energy source, such as mixtures of palmitic acid, stearic acid, and oleic acid ($2C_{51}H_{98}O_6$), the RER is about .70 ($VCO_2/VO_2 = 102/145 = .70$).

$$2C_{51}H_{98}O_6 + 145O_2 \text{ -----> } 102CO_2 + 98H_2O$$

Consequently, the RER ranges from .70-1.00, with the lower end of the range indicating a greater fat contribution (deVries, 1986; Brooks and Fahey, 1984).

Protein is the only other nutrient that is able to provide energy for muscular contraction. The relative contribution of the three possible energy sources, carbohydrate, fat, and protein, depend on the exercise intensity as well as the fitness and the nutritional status of the individual (Hasson and Barnes, 1989). Protein is not used as fuel to any appreciable extent at rest or during any exercise intensity, unless the individual is nutritionally impaired (Åstrand and Rodahl, 1986). Hedman (1957) demonstrated that during exercise, in an individual with normal nutritional status, nitrogen excretion was not significantly increased, as it would be if protein was being used as a fuel. Proteins are used almost exclusively to replace damaged cell parts.

Thus, the nonprotein RER is used to examine the relative contribution of carbohydrates and fats as fuel sources for the body.

Niacin

Niacin, nicotinic acid, or antipellagra vitamin, is a water soluble vitamin in the B complex. It is a whitish crystalline solid that can easily be converted to the physiologically active compound nicotinamide. Both nicotinic acid and nicotinamide are stable in the dry state and soluble in water, although nicotinamide has a much higher solubility. Nicotinic acid is remarkably resistant to heat, light, air, acids, and alkalies (Krause and Mahan, 1984; Pike and Brown, 1986; Williams, 1988).

Sources of Niacin

Niacin is found in a variety of common foods and can also be synthesized in the body from the essential amino acid tryptophan. Therefore, the RDA for niacin is expressed in niacin equivalents (NE). Since it takes 60 mg of tryptophan to produce 1 mg of niacin, one NE equals 1 mg of niacin or 60 mg of tryptophan. Excellent sources of niacin include lean meats, poultry, and fish since they are all rich in both niacin and tryptophan. Sources rich in niacin alone are organ meats, brewer's yeast, peanuts, and peanut butter. Milk and eggs contain large amounts of tryptophan. Smaller amounts of niacin and tryptophan may be found in beans, peas, other legumes, nuts, and enriched whole-grain cereal products. The RDA for niacin is 6.6 mg/1,000 kcal (16-19 NE for adult males and 13-14 NE for adult females) (Krause and Mahan, 1984; Williams, 1988).

Niacin Absorption and Storage

Niacin absorption occurs in the intestine except for forms in fortified cereals that are bound and not available for absorption. Excess niacin, very little being stored, is eliminated through the urine (Krause and Mahan, 1984).

Niacin Functions

Niacin is important in the metabolic processes of supplying the body with energy. Niacin functions as a component of two coenzymes that are essential to glycolysis, fat synthesis, and respiratory mechanisms of all cells. The two coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), have such widespread involvement that the lack of niacin causes major damage to cellular respiration. Both NAD and NADP are involved in oxidation-reduction reactions (transfer of electrons and hydrogens) serving as hydrogen acceptors in energy metabolism. The reduced state is designated NADH and NADPH. In cellular respiration, responsible for energy release, NADH usually transfers its hydrogen to flavine adenine dinucleotide (FAD). In contrast, NADPH regularly donates its hydrogen to cellular biosynthetic processes such as the synthesis of FFA (Krause and Mahan, 1984; Pike and Brown, 1986; van der Beek, 1985).

The list of enzyme systems that the coenzymes NAD and NADP are involved in is long. The coenzyme NAD participates in the enzyme systems of many enzymes including alcohol dehydrogenase, glycerophosphate dehydrogenase, lactate dehydrogenase, and glyceraldehyde-3-phosphate dehydrogenase. Isocitrate and glutamic dehydrogenase can use either NAD or NADP, whereas, NADP (in NADPH

form) is involved with malic enzyme and glucose-6-phosphate dehydrogenase (Pike and Brown, 1986).

Nicotinic Acid Doses

Large doses of nicotinic acid have been used for a wide variety of purposes including as an ergogenic aid (Frankau, 1943; Hilsendager and Karpovich, 1964), to treat schizophrenia (Osmond and Hoffer, 1962), to treat pellagra (Krause and Mahan, 1984), to examine the effects on bouts of exercise (Bergström et al., 1969; Carlson et al., 1963), to reduce plasma FFA levels (Hanson et al., 1965; Martineau et al., 1989), and most commonly as an anticholesterol agent (Alderman, et al., 1989; Atmeh et al., 1983; The Coronary Drug Project Research Group, 1975; Gurakar et al., 1985; Hanefeld et al., 1984; Hoogerf et al., 1984; Shepherd et al., 1979).

The amount of the nicotinic acid dose and the time for treatment varies considerably for the purposes mentioned above. As a possible ergogenic aid, Hilsendager and Karpovich (1964) used two 75 mg nicotinic acid doses and Frankau (1943) used three days of a 40 mg dose of nicotinamide. Osmond and Hoffer (1962) reported use of up to 5 g/day for extended periods in the treatment of schizophrenia. Administration of 150-600 mg/day has been reported in severe cases of pellagra (Krause and Mahan, 1984).

Of particular interest to the present project are the amounts of nicotinic acid used to affect substrate utilization during bouts of exercise, to affect plasma FFA levels, and to affect cholesterol levels. Two investigations demonstrated significant changes in RER with infusion of 1.4 g of nicotinic acid over four hr of rest and

exercise (Carlson et al., 1963) and 1.6 g (1 g IV and 600 mg orally) of nicotinic acid given in a two hr period prior to exercise (Bergström et al., 1969). Two other studies reported significant decreases in plasma FFA levels with ingestion of 200 mg of nicotinic acid 10 min prior to testing (Hanson et al., 1965) and 3.2 $mg \cdot kg^{-1}$ (235 mg for 70 kg person) 2 hr prior to testing with 1.6 $mg \cdot kg^{-1}$ administered every 30 min thereafter (Martineau and Jacobs, 1989).

A variety of nicotinic acid doses, progressions of doses, and durations of nicotinic acid treatment have been used to achieve similar changes in plasma cholesterol levels. The doses vary from 1.2 g/day (Hanefeld et al., 1984) to 4 g/day (Hanefeld et al., 1984) with the most common dose being 3 g/day (Coronary Drug Project Research Group, 1975; Gurakar et al., 1985; Grundy, Mok, Zech and Berman, 1981; Hoogwerf et al., 1984; Shepherd et al., 1979). The investigators varied in how fast they increased the dose of nicotinic acid to the target dose. One group of researchers increased the dose from .5 g/day to 3 g/day in 3-6 days (Hoogwerf et al., 1984) and another group took 6 months to increase from 1 g/day to 3 g/day (The Coronary Drug Research Group, 1975). Table 1 contains the information comparing nicotinic acid dose and effect for the studies reviewed.

Tolerance of Nicotinic Acid

Large doses of nicotinic acid have been used to bring about changes in cholesterol levels for over 40 years (Altschul et al., 1955) despite annoying side effects. Flushing, a reddening of the skin with the sensation of heat or itching, is the most common side effect. This flushing response mainly affects the upper body and

Table 1

Nicotinic Acid Dose, Progression of Dose, Duration of Dose, and Effect of Dose in Exercise and Cholesterol Studies

Principle Investigator	Dose(g)	Progression	Duration	Effect
Hanson ('65)	.2		once	decrease FFA
Martineau ('89)	.24 & .12 every .5 hr		once	decrease FFA
Bergström ('69)	1.6		once	increase RER
Carlson ('63)	1.4 (over 4 hr)		once	increase RER
Jenkins ('65)	.2 & .1 hr later		once	increase RER
Alderman ('89)	1.4 $\pm$ .7 g/d	100-250 mg increased to target in 4-8 wk	11$\pm$7 mo	decrease chol increase HDL
Coronary ('75)	3 g/d	1 g/d 1 mo 2 g/d 1 mo	5 yr	decrease chol no diff in mortality
Hanefeld ('84)	1.2-4 g/d		25$\pm$8.3 mo	decrease chol
Hoogwerf ('84)	3 g/d	.5 g/d to 3 g/d in 3-6 days	12 wk	decrease chol increase HDL
Shepherd ('79)	3 g/d		3 wk	decrease chol increase HDL

face occurring 1 to 2 hr after ingestion and the symptoms usually disappear after repeated nicotinic acid administration. Flushing, which may reappear intermittently even in adapted individuals, may be decreased by increasing the dose slowly, ingesting nicotinic acid with meals, and prior administration of aspirin. Reduced oral glucose tolerance is also common with ingestion of nicotinic acid. The oral glucose tolerance test, a method used to diagnose diabetes, assesses the ability of the body to adapt to a glucose load (Krause and Mahan, 1984). Other less common possible risks include liver dysfunction and gastrointestinal stress. However, these risks are very low when dealing with young, healthy individuals (Malinow, 1986).

Kane et al. (1981) were first to document that patients who took aspirin before nicotinic acid administration could decrease the flushing response. Nicotinic acid and salicylic acid both undergo glycine conjugation; thus it appears that competitive inhibition occurs when both substances are ingested at the same time. Ding and co-authors (1989) hypothesized that salicylic acid causes a decrease of total nicotinic acid clearance that results in the saturation of the nicotinuric acid conjugation pathway. Therefore, aspirin, when taken with nicotinic acid, not only mitigates the flushing response but also allows increased bioavailability of nicotinic acid because of the higher and prolonged plasma concentrations of nicotinic acid for a given dose. Time-release forms of nicotinic acid were developed in an attempt to relieve the flushing response, although these forms actually caused a more severe reaction (Knopp, 1989; Knopp et al., 1985).

Investigations Using Nicotinic Acid

Nicotinic acid has been used in a number of investigations for a variety of reasons. The studies involving nicotinic acid (niacin) include: (a) effects on fuel utilization at rest, (b) effects on fuel utilization during bouts of exercise, and (c) effects on cholesterol levels.

Nicotinic Acid Effects on Fuel Utilization at Rest

Numerous investigators have demonstrated changes in FFA mobilization as a result of ingesting or infusing nicotinic acid. The articles that were reviewed all indicated that plasma or serum FFA levels were lowered by the presence of nicotinic acid.

Havel, Carlson, Ekelund and Holmgren (1964) investigated the effects of norepinephrine and nicotinic acid on energy metabolism in seven 21-26 year old subjects. The subjects ingested 1-3 g of nicotinic acid daily for 3 days before the testing, to accustom them to the flushing response caused by nicotinic acid, and then reported to the laboratory at 0800 hr after a 12-15 hr fast. During the entire procedure (just over 4 hr) the subjects were supine with a catheter in an antecubital vein and a brachial artery while expired air was collected intermittently. Norepinephrine was infused between minutes 45 and 60 and plasma concentrations of FFA, glycerol, and glucose rose rapidly. At minute 120, nicotinic acid (100 or 200 mg) infusion started at 15 min intervals up to minute 225, when another infusion of norepinephrine started. The plasma concentration of FFA, glycerol, and glucose

decreased after the first infusion of nicotinic acid and stabilized in 30 min. The RER was increased after administration of nicotinic acid. The effect of norepinephrine on FFA and glycerol levels was almost completely blocked by nicotinic acid.

Two groups of investigators took advantage of the decreasing plasma levels of FFA caused by administration of nicotinic acid to investigate cold exposure in man. Hanson et al. (1965) used four males (aged 21-25 years) to examine the effects of nicotinic acid ingestion on plasma FFA in acute cold exposure in a fasted state. A 200 mg dose of nicotinic acid was taken 10 min before the start of the cold exposure. The plasma FFA level was significantly lower in the conditions of the experiment that involved ingestion of nicotinic acid. More recently, Martineau and Jacobs (1989) also investigated plasma FFA levels using nicotinic acid although the cold exposure was in water. Eight males (aged 19-32 years) performed two cold water immersions one week apart following a 14-16 hr fast. Both immersions were preceded by ingestion of nicotinic acid or placebo (3.2 $mg \cdot kg^{-1}$ 2 hr prior to immersion and 1.6 $mg \cdot kg^{-1}$ at 30 min intervals before immersion). Plasma FFA levels were significantly lower before and during immersion in the trials with previous ingestion of nicotinic acid. The plasma FFA values with nicotinic acid ingestion were still significantly less than without nicotinic acid ingestion after immersion despite a 73% increase in FFA levels.

These findings demonstrate that nicotinic acid has a significant effect on fat utilization at rest. Butcher, Baird and Sutherland (1968) revealed the manner by which nicotinic acid effectively suppresses fat metabolism. Adenosine 3', 5'-monophosphate (cyclic AMP) has been implicated as an intracellular second

messenger. A decrease in cyclic AMP, caused by nicotinic acid, blocks the breakdown of white adipose tissue triglycerides to FFA and glycerol. Madsen and Malchow-Moller (1983) stated that nicotinic acid inhibited the stimulation of adenylcyclase in adipocytes, causing decreased intracellular concentrations of cyclic AMP, which interfered with the activation of hormone sensitive lipase. Nicotinic acid also has a direct inhibiting effect on the hormone sensitive lipase.

Nicotinic Acid Effects on Fuel Utilization During Bouts of Exercise

Three investigations have focused on the effects of nicotinic acid administration on exercise metabolism. The common findings of the three studies was that nicotinic acid decreased fat utilization in a variety of exercise conditions.

In 1963 Carlson and co-workers investigated the effect of nicotinic acid on the oxidation and turnover of FFA at rest and during exercise. The effect of nicotinic acid was compared to that of glucose since glucose also blocks mobilization of FFA during exercise. Four healthy men (aged 19-26 years) reported to the laboratory at 0800 hr after a 12-15 hr fast. Catheters were inserted in a brachial artery and two brachial veins in the opposite side and a constant infusion of labeled palmitic acid was started. After a 1 hr rest period, the subjects exercised on a cycle ergometer at a heart rate of 130 beats·min^{-1} for 2 hr and rested for an additional 1 hr. Two subjects were infused with a 20% glucose solution, which corresponded to the approximate energy cost of the exercise and the other two subjects were infused with 200 mg of nicotinic acid in the middle of the first rest period, followed by 100 mg of nicotinic

acid every 15 min throughout the 2 hr of exercise and the following 1 hr of rest. Prior to testing, the nicotinic acid subjects had an adaptation period of 4-5 days of taking .1 g of nicotinic acid 3 times/day and increasing the dose .3 g each day (final dose being 1-1.3 g three times/day). Expired air and blood samples were collected intermittently. The results of the four subjects were compared with those found in six fasting control subjects.

The results demonstrated that both nicotinic acid and glucose decreased the concentration and turnover rate of FFA and profoundly inhibited the usual increase in concentration and turnover rate found in fasted subjects during exercise of fasted subjects. The normal increase in concentration of glycerol in fasted exercise was not present in the glucose-infused subjects and one of the nicotinic acid-infused subjects. In the other nicotinic-acid infused subject, there was an increase in glycerol concentration and turnover rate of FFA during exercise, although the absolute values were lower than the control subjects. The plasma glucose concentration did not change significantly in the control subjects. In the glucose-infused subjects, the plasma concentration of glucose rose rapidly during the first hour and then decreased during exercise before rising again during the last rest period. The subject that demonstrated the greatest decrease in turnover rate of FFA had a large drop in the plasma glucose concentration (105 to 68 mg/100 ml) at the end of exercise while the other nicotinic acid-infused subject had little change. Both nicotinic acid-infused subjects had higher plasma glucose concentrations than the control subjects. The RER was higher during exercise and rest in the glucose-infused subjects. Until the last

hour of rest, the nicotinic acid-infused subject, who had the lowest glucose level during exercise, had a higher RER than the control subjects. After administration of nicotinic acid, the other subject demonstrated a progressive rise in RER to a higher level than the control subjects at the end of exercise. The levels of lactate and pyruvate in the nicotinic acid-infused subjects changed very little during exercise and were comparable to the values of the control subjects.

The most noteworthy results of the study were that nicotinic acid markedly decreased the rate of FFA mobilization at rest and inhibited the normal increase in FFA mobilization which occurs when fasted subjects exercise.

Jenkins (1965) investigated the effects of exhaustive exercise on metabolism with and without prior administration of nicotinic acid. Two males were exercised for 1.5 hr and one male for 2.5 hr at 10% grade and 3.5 mph following a 15 hr fast. Expired air and blood samples were collected at the basal state and further samples were taken at 30 min intervals of exercise and then 1 hr after exercise. A second exercise session was performed on another day which replicated the procedures of the first except that 200 mg of nicotinic acid was taken orally at the start of the exercise and a 100 mg dose an hour later.

The results indicated that blood glucose decreased significantly from the basal level with and without prior administration of nicotinic acid, although after nicotinic acid the values were significantly higher ($\underline{M}$ = 10 mg) than in the control run. After nicotinic acid administration, the FFA levels were unchanged, whereas they showed the normal rise in the control exercise, and the difference between them was

significant. The RER was significantly higher during the nicotinic acid exercise, with a mean difference of .05 RER units (.867 and .916). One hour after the exercise bout, the differences between the nicotinic acid administration session and the control session were in opposite directions. In the nicotinic acid exercise recovery, the blood-glucose level fell more, two subjects showed a rise in FFA levels, and the RER fell to lower levels.

The RER and blood-glucose levels during exercise were higher after administration of nicotinic acid than in the control exercise. The increased RER was an indication of increased carbohydrate metabolism.

Bergström et al. (1969) examined the effect of nicotinic acid on physical work capacity with particular focus on the possibility of increased glycogen utilization when nicotinic acid blocked mobilization of FFA. Fifteen males (aged 20-33 years) who were trained but not competing, reported to the laboratory in the morning after a 13-15 hr fast. In the first series, two subjects performed a two-leg cycle ergometer protocol that started at 300 $kgm \cdot min^{-1}$ and increased 300 $kgm \cdot min^{-1}$ every 6 min up to a near maximal level. After a 2 hr rest, during which 1.6 g of nicotinic acid (1 g IV and .6 g orally) was given, the two subjects performed the same procedure. In the second series 13 subjects used one-leg cycle ergometry at a constant load of 250-400 $kgm \cdot min^{-1}$. The sequence of legs was randomized and each leg was worked for 60-90 min with a 1 hr rest period in between. Catheters were inserted into the brachial artery and both femoral veins for both cases in the first series and 7 of the 13 cases in the second series for blood draws before and at the end of each exercise period. A

needle biopsy was used to collect a sample from the quadriceps femoris muscle before and after exercise (also after 45 min in subjects cycling for 90 min) in the second series. Expired air was collected for 5 min periods at rest and 3 min periods during exercise and heart rate was recorded from an ECG.

When the work was gradually increased to a near maximal level in the first series, the subjects performed the same amount of exercise whether nicotinic acid was administered or not. After nicotinic acid administration, the RER was higher at rest and at lower work loads, although there was no difference in RER at higher work intensities. Arterial lactate and glucose concentrations were lower in the nicotinic acid exercise.

In the second series, where the opposite leg was used for the nicotinic acid exercise, the subjects performed the same amount of work, although the second bout of exercise was more fatiguing. The resting heart rate was similar before the two exercise sessions, however, the increase in heart rate during exercise before nicotinic acid administration was significantly higher with a mean difference of 20 beats·min^{-1} at the end of the exercise. The VO_2 was slightly higher in the cycling with prior administration of nicotinic acid ($p < .10$). The RER was slightly higher at rest in the nicotinic acid condition, but was significantly ($p < .005$) higher at the end of exercise in the nicotinic acid trial (.93 $\pm$ .03 [SD] to .77 $\pm$ .03). There was an increased rate of glycogen utilization after administration of nicotinic acid both at 45-60 min of exercise ($p < .025$) and after 90 min of exercise ($p < .005$). Arterial glucose had large individual variations and was less at rest after nicotinic acid administration and

showed no differences during exercise. The lactate concentration was significantly higher during exercise after nicotinic acid administration. The resting levels of FFA were lower after nicotinic acid in four of five subjects and the normal increase during exercise was almost completely blocked. One nicotinic acid-administered subject showed an increase in FFA concentration with exercise, although the values were lower than the control exercise. The glycerol concentration was lower after nicotinic acid administration both at rest and during exercise.

Bergström and co-authors (1969) demonstrated that large doses of nicotinic acid decreased the mobilization of FFA from adipose tissue, evidenced by the low arterial concentration of FFA and glycerol during the second series of nicotinic acid exercise. An increase in carbohydrate utilization, to compensate for the decreased fat utilization during the nicotinic acid condition was evidenced by an increased rate of glycogen utilization and higher RER values. Carlson et al. (1963) and Jenkins (1965) both reported similar findings with respect to this increase in carbohydrate utilization to compensate for the decrease in oxidation of FFA caused by administration of nicotinic acid.

Nicotinic Acid Effects on Cholesterol Levels

The evidence to demonstrate that nicotinic acid treatment has a profound effect on cholesterol levels is widespread (Alderman et al., 1989; Atmeh et al., 1983; Blankenhorn et al., 1987; The Coronary Drug Project Research Group, 1975; Glueck, 1985; Gurakar, 1985; Hanefeld et al., 1984; Kane et al., 1981; Shepherd et al.,

1979). The results of the research generally indicate a decrease in total cholesterol, an increase in high density lipoprotein (HDL) cholesterol, and a decrease in the cholesterol to HDL ratio as a result of the administration of pharmacologic doses of nicotinic acid. The importance of altering the cholesterol levels is evidenced by the relationship between cholesterol levels and coronary artery disease (CAD). Many research groups have established a high correlation between total cholesterol and CAD (Carlson and Bottiger, 1972; Hanefeld et al., 1984; Kannel, Castelli and Gordon, 1979; Robertson et al., 1977; Shekelle et al., 1981). In addition, the levels of HDL have an inverse relationship with CAD (Gordon, Castelli, Hjortland, Kannel and Dawber, 1977; Gotto, 1983; Lewis, 1983; Miller, Thelle, Forde and Mjos, 1977; Uhl, Troxler, Hickman and Dale, 1981) and the ratio of cholesterol to HDL has been reported to be highly predictive of CAD (Arntzemins et al., 1985; Lipid Research Clinics Program, 1984; Uhl et al., 1981)

There are three studies that clearly show the effect of nicotinic acid treatment alone on cholesterol. Alderman et al. (1989) recruited 101 patients, 86 men and 15 women, from 36-73 years old, who had clinically documented CAD. Nonfasting baseline total cholesterol and HDL values were obtained on at least two separate days before beginning the niacin treatment. The niacin dose started at 100 or 250 mg two times/day and was increased as tolerated in 4-8 weeks to 1 g twice daily. The average dose of niacin for all subjects was 1,415 $\pm$ 698 mg/day (range of 200-4000 mg). Total cholesterol and HDL levels were again determined at 6 weeks and then every 3-6 months. The subjects were followed for a mean duration of 11 $\pm$ 7 months with a

range of 2-34 months. The entire group had a 13% decrease in total cholesterol ($p < .001$), 31% increase in HDL ($p < .001$) and 32% decrease in the cholesterol to HDL ratio. The 62 subjects who tolerated at least 1,000 mg/day of niacin had an 18% decrease in total cholesterol (246 ± 46 to 202 ± 48 mg·dl^{-1}, $p < .001$), HDL rose by 32% (37 ± 10 to 49 ± 14 mg·dl^{-1}, $p < .001$) and the total cholesterol to HDL ratio improved 36% (6.9 ± 1.9 to 4.4 ± 1.3, $p < .001$). The rest of the subjects ($n = 39$), who tolerated less than or equal to 1,000 mg/day of niacin, only had a 5% reduction in total cholesterol, although there was a significant ($p < .001$) 29% increase in HDL, which led to a significant ($p < .001$) decrease in the total cholesterol to HDL ratio.

Hoogwerf and co-authors (1984) researched the effects of nicotinic acid treatment on patients with type III hyperlipoproteinemia, which may be associated with hypercholesterolemia and hypertriglyceridemia. Five males with a mean age of 49 years (range 29-59 years) participated in the study. After a 6 week period for baseline measurements, each subject started at .5 g/day of nicotinic acid and increased to 3 g/day in 3-6 days for 12 wk. The results indicated a significant reduction (28%) from baseline in total cholesterol, a significant ($p < .001$) increase (28%) in HDL cholesterol and HDL to LDL (low density lipoprotein) ratio (62%).

Shepherd et al. (1979) investigated the effects of 3 g/day of nicotinic acid for 3 weeks on five (3 male, 2 female) healthy young adults (aged 23-29 years). Baseline cholesterol measures were made before the nicotinic acid administration period and measures were taken after the 3 week treatment. Nicotinic acid decreased plasma

cholesterol (15%) and also significantly raised plasma HDL cholesterol levels (23%).

Effects of Exercise on Cholesterol Levels

Exercise such as walking, jogging, swimming, cycling, and cross-country skiing that use large muscle groups in a continuous and rhythmic pattern are oxygen-dependent or aerobic in nature. Regular involvement in these continuous types of activities have been associated with improvements in lipid-lipoprotein profiles (Goldberg, 1989). Several authors have suggested that regular endurance activity increases the concentration of HDL cholesterol (Farrell et al., 1982; Schnabel and Kindermann, 1982; Wood and Haskell, 1979).

A number of additional cross-sectional investigations have reported that endurance-trained individuals exhibit more favorable lipid-lipoprotein profiles than sedentary counterparts. These studies include elite distance runners (Martin, Haskell and Wood, 1977; Wood, Haskell, Stern, Lewis and Farquhar, 1976), competitive cross-country skiers (Enger, Herbjornsen, Eriksen and Fretland, 1977) and middle-aged male joggers (Penny, Shaver, Carlton and Kendall, 1982). Cross-sectional studies have the disadvantage of the inability to account for factors that may influence a subject's lifestyle. For example, subjects who have desirable cholesterol levels may more often choose a lifestyle that includes exercise compared to subjects with poor lipid-lipoprotein profiles. Longitudinal training studies can eliminate this problem of the possibility of the choice of a life style that includes exercise because of desirable cholesterol levels.

Longitudinal training studies have reported some variability in results regarding

the effect of endurance exercise on cholesterol levels. A number of research groups have reported a favorable change in cholesterol levels as a result of endurance exercise (Farrell and Barboriak, 1980; Heath et al., 1983; Hespel et al., 1988; Rotkis et al., 1984; Wood et al., 1983), whereas others have not demonstrated significant changes in cholesterol levels (Lipson, Bonow, Shaefer, Brewer and Lindgren, 1980; Raz, Rosenblit and Kark, 1988; Williford, Blessing, Barksdale and Smith, 1988).

Heath and co-authors (1983) conducted a training investigation with 10 men (aged 46-62 years) who had CAD. The subjects trained on a track or a cycle ergometer at 50-85% of VO_2 max for 40-60 min, 3-5 days/week for 29 $\pm$ 7 weeks. The training significantly increased VO_2 max (31 $\pm$ 19%, $p < .001$), decreased plasma cholesterol (-8 $\pm$ 4%), and increased HDL cholesterol levels (11 $\pm$ 13%). The authors concluded that the beneficial changes in cholesterol appeared to be due to a training effect since they correlate best with changes in VO_2 max.

In a study with a healthy population, Farrell and Barboriak (1980) endurance trained 16 subjects (7 male, 9 female) for 8 weeks at 70% VO_2 max, 30 min/day for 3-4 days/week. Plasma lipoprotein concentrations were assessed prior to training and at 2 week intervals. After a nonsignificant decline at 2 weeks, HDL cholesterol concentration increased significantly from 51.1 to 57.4 $mg \cdot dl^{-1}$ after 8 weeks of training showing a similar change in males and females. The relationship between HDL cholesterol and triglycerides was significant ($r = -.65$) during the last 4 weeks of training, indicating a parallel between the decline in plasma triglycerides and an increase in HDL cholesterol levels. A similar study, with a longer duration, was

reported by Hespel and others in 1988. Twenty seven healthy sedentary men (aged 20-55 years) participated in endurance training, 1 hr 3 times/week, which consisted of 25 min of cycle ergometry, followed by 5 min of rest, 15 min of jogging, 5 min of rest, and 10 min of dynamic calisthenics. Thirteen subjects participated in the training program the first four months while the other 14 served as controls. Then the control subjects completed the same training program. With training, both groups significantly increased physical work capacity, significantly increased HDL cholesterol, and significantly decreased total cholesterol.

In a very well-controlled longitudinal study, Wood et al. (1983) randomly assigned 81 sedentary but healthy men (aged 30-55 years) to a running program ($\underline{n}$ = 48) or to serve as sedentary controls ($\underline{n}$ = 33). The exercise consisted of calisthenics and stretching, a 5 min warm-up of walking or slow jogging, a 25 min run at 70-85% of capacity, and a 5 min cool down. Between week 2 and 3, the subjects added a fourth day of exercise and by week 8-10 a fifth day was added. After 1 year, the running group had lipoprotein concentration changes that favored a reduced risk of CAD, although the changes were not significant when all 46 runners were analyzed. However, there was a significant increase ($\underline{p}$ = .045) in HDL levels by 4.4 $mg \cdot dl^{-1}$ when the 25 men who averaged at least 8 mi/week were analyzed separately. The authors concluded that there appears to be an 8 mi/week threshold where a 1-year running program leads to beneficial changes in cholesterol levels.

Rotkis et al. (1984) solicited the participation of 19 females (aged 24-37 years) in a 15 month endurance training program to assess the effects of running on plasma

total cholesterol and HDL cholesterol. The dropout rate was controlled by selecting women who already were running 15.1 mi/week. The subjects were asked to run 5-6 days/week and to gradually increase weekly mileage without regard to speed. Blood samples were taken after the subjects had increased their mileage by 30 mi/week above baseline for two straight weeks and again when they increased their mileage by 50 mi/week above baseline for two consecutive weeks. The results indicated no change in total cholesterol, although there were significant ($p < .001$) increases in HDL cholesterol levels from 59.6 $mg \cdot dl^{-1}$ at baseline to 63.7 $mg \cdot dl^{-1}$ and 69.4 $mg \cdot dl^{-1}$ at +30 and +50 mi/week, respectively.

Other researchers have not reported beneficial changes in cholesterol levels as a result of endurance training. Williford and co-workers (1988) used 10 weeks of aerobic dance training on 10 healthy, untrained females (M = 23 years old) to investigate changes in lipoprotein levels. The training consisted of 5-10 min of warm-up and stretching, 30 min of aerobic dance at 60-90% of heart rate reserve, and a 7 min cool-down. Although cardiovascular fitness improved, total cholesterol (177 ± 27 to 179 ± 19 $mg \cdot dl^{-1}$) and HDL cholesterol (51 ± 12 to 53 ± 12 $mg \cdot dl^{-1}$) levels did not change.

Lipson et al. (1980) reported that there were no significant changes in HDL cholesterol levels, although total plasma cholesterol decreased significantly (156 to 140 $mg \cdot dl^{-1}$) in a 6 week exercise conditioning program. The study consisted of of 5 females and 5 males (aged 19-22 years) who trained on a treadmill for 30 min/day at 70% of VO_2 max. Weight was maintained by feeding the subjects a specified diet.

The last study reviewed that did not report any changes associated with an endurance training program was conducted by Raz and co-authors (1988). Fifty-five healthy, sedentary, nonobese males (aged 24-26 years) underwent a 9 week training program of 5 min warm-up, 45 min of supervised exercise (jogging or aerobic circuit training) at 70-85% of VO_2 max, and a 5 min cool-down at two times/week. Once a week subjects exercised (jogging, biking, or swimming) on their own for 60 min. When compared to controls, the exercise group demonstrated no significant changes in total cholesterol or HDL cholesterol levels.

There appears to be evidence for and against the suggestion that exercise has a beneficial effect on lipid levels. The question of these inconsistencies was investigated by Tran and Weltman (1985) in a meta-analysis of 95 investigations on the effect of exercise on serum lipid and lipoprotein levels. The meta-analysis revealed that the changes in body weight as a result of an exercise program may obscure the effects of the endurance training on beneficial changes in cholesterol levels. Previous research has demonstrated that decreases in body weight have a significant effect on reducing total cholesterol (Brownell and Strunkard, 1981; Streja, Boyko and Rabkin, 1980; Zimmerman et al., 1984). It is difficult to interpret the results of the studies reviewed because the authors did not publish the weight of the subjects before and after the training program. In addition to the factor of weight changes, Tran and Weltman (1985) concluded that beginning cholesterol levels were important in the ability of the training to change cholesterol levels. Individuals with high beginning cholesterol levels were more likely to have changes as a result of an exercise program. In this

limited review, only one investigation reported decreasing previously low total cholesterol levels (156 $mg \cdot dl^{-1}$) to even lower values (140 $mg \cdot dl^{-1}$) (Lipson et al., 1980).

Summary

Nicotinic acid or niacin, a water soluble vitamin in the B complex, has been used in a wide range of doses for a number of purposes, including: (a) to reduce plasma FFA levels, (b) to change cholesterol levels, and (c) to examine the effects on bouts of exercise. Several investigations have reported decreased fat utilization, assessed by indirect calorimetry using the RER and blood-borne substrate levels, both at rest and exercise with prior administration of nicotinic acid. The use of nicotinic acid to have a beneficial effect on lipid-lipoprotein profiles has continued since the 1950s and numerous investigations have reported favorable changes in cholesterol profiles with nicotinic acid treatment. Although the evidence is not conclusive, many investigators would suggest that exercise can also have a beneficial effect on cholesterol levels.

Nicotinic acid has proven to decrease fat utilization in bouts of exercise, although this phenomenon has not been investigated over a period of time where an adaptation may be evident. Some kind of adaptation to nicotinic acid would be apparent in the analysis of fuel utilization as measured by RER and blood-borne substrate levels. It was apparent, after a review of the literature, that an investigation of fuel utilization and blood-borne substrate levels during a nicotinic acid treatment period would provide new and valuable information about the ability of the body to

adapt to nicotinic acid administration over time.

CHAPTER III

METHODS

The purpose of this study was to investigate the changes in substrate utilization and blood-borne substrate levels during 30 min of submaximal treadmill running at the start, mid-point, and end of a three week period during which pharmacologic doses of nicotinic acid were being ingested. A description of the procedure used to obtain and analyze the experimental data is contained in this section. The section is organized as follows: (a) subject selection, (b) design, (c) instrumentation, (d) testing procedures, and (e) statistical analysis.

Subject Selection

The subjects were eight male volunteers between the ages of 18 and 41 years who habitually exercised. The subjects met the requirements of a maximal oxygen consumption ($\dot{V}O_2$ max) of approximately 60 $ml \cdot kg^{-1} \cdot min^{-1}$ and a regular training program consisting of a minimum 20 min of continuous exercise at least three times per week.

The only inducements offered to the subjects to participate were the results of the study. An informed consent document (Appendix A) and a medical questionnaire

(Appendix B) was read, completed, and signed by each subject before participation. The study complied with the conventions for the ethical treatment of subjects as described in *Medicine and Science in Sports and Exercise* (1990) and was approved by the Oregon State University Institutional Review Board for use of Human Subjects.

Design

The design of the investigation was quasi-experimental using a within-subjects analysis. The respiratory exchange ratio (RER) value and the blood parameters assessed during the 30 min run procedure were dependent variables. The nicotinic acid supplement represented the independent variable. The subjects' age, height, weight, VO_2 max, and percent body fat were compared to describe the homogeneity of the group. The subjects first performed a VO_2 max test which was followed by two 30 min submaximal runs at 6 mph (approximately 60% VO_2 max) at 3 and 5 days after the maximal test, respectively. Each submaximal run was performed after a 12 hr fast period. The second submaximal run was performed one hour after the ingestion of a 1 g dose of nicotinic acid. Then 21 days of nicotinic acid ingestion (starting with 100 mg taken three times/day) followed. The nicotinic acid dose was taken three times/day and the dose was increased by 100 mg/day during days 2-10, at which time the subjects reached the target dose of 1 g taken three times/day. On Day 11 the subjects performed another 30 min submaximal treadmill run. The target dose of 3 g/day continued until Day 21 when the last 30 min submaximal test was conducted (Table 2 and Figure 1). The progression of increase in the nicotinic acid dose was a compromise between the Hoogwerf et al. (1984) approach of increasing

Table 2

Subject Procedures

Pre-Nicotinic Acid (NA) Treatment

Day 1 -- VO_2 max test

Day 3 -- 30 min run (6 mph)

Day 5 -- 30 min run (6 mph) after ingesting 1 g NA 1 hr prior

NA Treatment

Day 1 -- 100 mg NA 3 times/day (1 dose before exercise)

2 -- 200 mg NA 3 times/day (1 dose before exercise)

3 -- 300 mg NA 3 times/day (1 dose before exercise)

4 -- 400 mg NA 3 times/day (1 dose before exercise)

5 -- 500 mg NA 3 times/day (1 dose before exercise)

6 -- 600 mg NA 3 times/day (1 dose before exercise)

7 -- 700 mg NA 3 times/day (1 dose before exercise)

8 -- 800 mg NA 3 times/day (1 dose before exercise)

9 -- 900 mg NA 3 times/day (1 dose before exercise)

10 -- 1 g NA 3 times/day (1 dose before exercise)

Day 11 -- 30 min run (6 mph) after ingesting 1 g NA 1 hr prior

Day 11-21 -- 1 g NA 3 times/day (1 dose before exercise)

Day 21 -- 30 min run (6 mph) after ingesting 1 g NA 1 hr prior

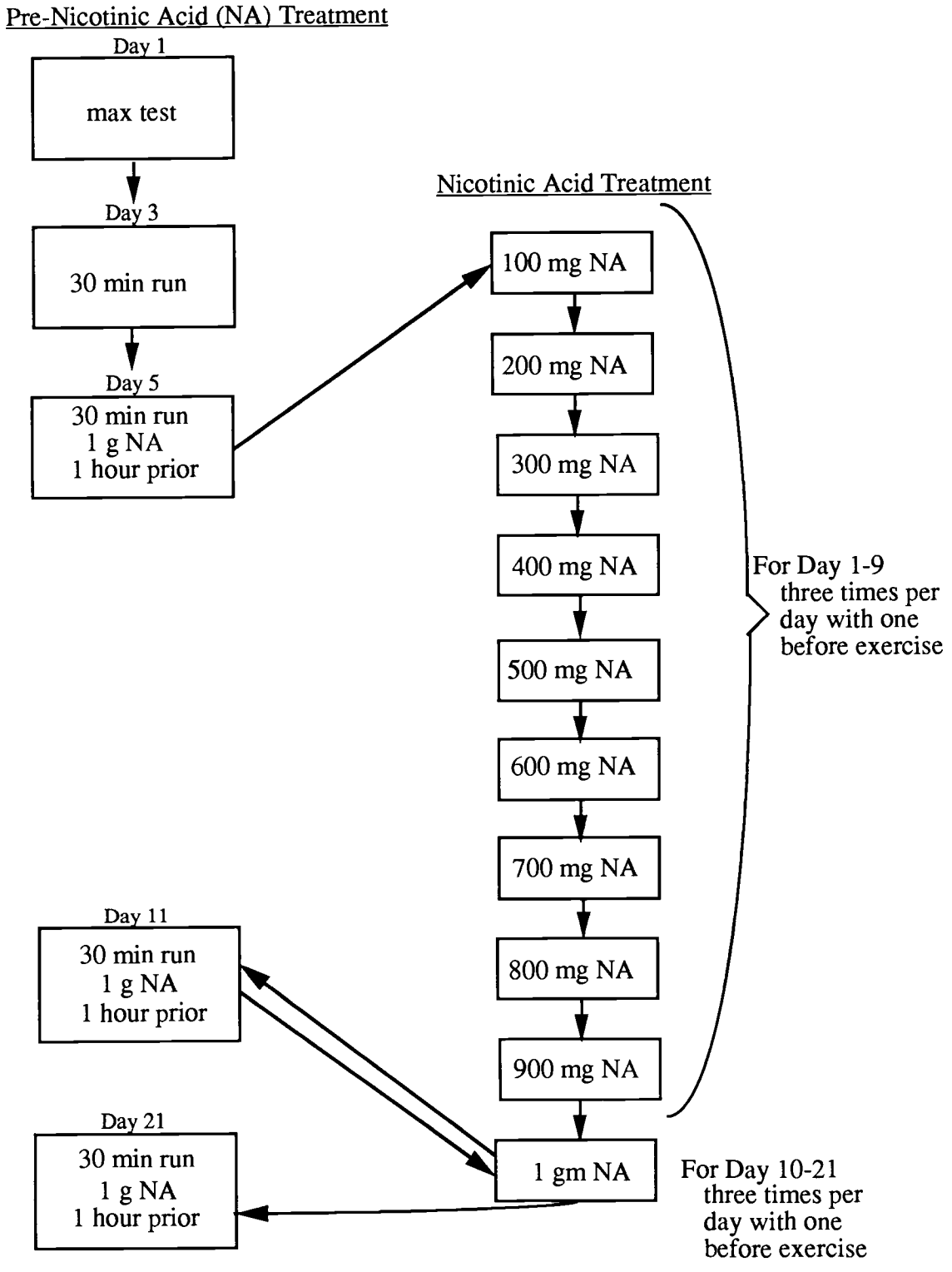


Figure 1

Subject Procedures

the dose to 3 g/day in 3-6 days and The Coronary Drug Research Groups (1975) method of increasing the dose to 3 g/day in 6 months.

Instrumentation

This study obtained descriptive data of the subjects by using a VO_2 max test and hydrostatic weighing.

Maximal Exercise Test

The maximal exercise test was performed on each subject to determine VO_2 max and the treadmill speed that elicited approximately 60-65% VO_2 max. Prior to the start of the incremental exercise test on the motor-driven treadmill, each subject was briefed on the methods involved in the testing. The subjects were encouraged to continue exercising until they reached the point of volitional fatigue.

Following a brief warm-up period for familiarization, the exercise test was initiated at 134 m/min (5 mph) and 0% grade. The speed was increased by 26.8 m/min (1 mph) at 2 min intervals until a constant speed of 188 m/min (7 mph) was attained and the slope was increased 2% every 2 min thereafter. The subjects were asked to exercise at increasing work rates, in accordance with the protocol, while oxygen consumption was measured.

The achievement of VO_2 max was substantiated by: (a) further increases in work rate not eliciting an increase in oxygen consumption, (b) a respiratory exchange ratio above 1.1, and (c) the heart rate approximating the age-predicted maximal heart rate (220 - age) (deVries, 1986). The test was stopped when the subject indicated that

he was too fatigued to continue. Heart rate, oxygen consumption, and blood pressure were monitored throughout the test.

The heart rate and ECG of the subjects were monitored using a CM5 electrode lead configuration (Ellestad, 1980). A hard copy of the ECG was made at rest and during the last 10 s of each minute of exercise.

The brachial artery auscultation technique was used to monitor blood pressure. Detection of blood pressure was accomplished using a Quinton Model 410 automatic blood pressure device which provides an accurate alternative to manual auscultation in young, healthy individuals (Lightfoot, Tankersley, Rowe, Freed and Fortney, 1989).

An open circuit indirect calorimetry technique was used to measure oxygen consumption on a minute-by-minute basis. Before each test, the oxygen and carbon dioxide analyzers were calibrated with a known gas mixture. After the subject was familiarized with the treadmill, the testing session began. Wearing a nose clip, the subject breathed through a valve connected to a mixing chamber on the exhalation side and a Parkinson Cowan Dry Gas Meter on the inhalation side. The exhaled air was drawn from the mixing chamber, through calcium sulfate ($CaSO_4$) cylinders, to an Applied Electrochemistry S-3A oxygen analyzer and a Beckman LB-2 carbon dioxide analyzer. Output from these gas analyzers and the ventilation meter was sent to an Apple II Plus microcomputer. Here appropriate digitation, integration, and reduction of the analog signals occurred so that values for $\dot{V}_E$ STPD ($l \cdot min^{-1}$), $\dot{V}O_2$ STPD ($l \cdot min^{-1}$), $\dot{V}O_2$ STPD ($ml \cdot kg^{-1} \cdot min^{-1}$), $\dot{V}CO_2$ STPD ($l \cdot min^{-1}$), FEO_2, $FECO_2$, and RER values were displayed on an Apple Monitor III CRT and an Epson printer with the use

of the Rayfield Software Program (1985). Before the test, appropriate environmental conditions were entered into the computer so corrections in the calculations of the metabolic data could be made.

Hydrostatic Weighing

After age, height, and weight were recorded, residual lung volume was estimated. Residual lung volume was assessed using a modification of the standard oxygen dilution technique that used a five-liter rebreathing bag (Wilmore, Vodak, Parr, Girandola and Billing, 1980). Body composition was then assessed by the use of hydrostatic weighing. Six to 10 trials were made for hydrostatic weighing with the mean of the two highest trials being used to compute the underwater weight (Weltman and Katch, 1981), following methods described by Katch, Michael, and Horvath (1967). A load cell had a PVC pipe platform suspended from it to record the underwater weight. The subjects exhaled maximally and then submerged while sitting on the platform. A 5 kg diver's weight belt was placed across the subject's lap in order to minimize platform movement and to counteract any buoyancy. Body density was determined using the formula of Brozek, Grande, Anderson and Keys (1963) and then the Siri formula (1956) was used to convert body density to percent body fat.

Submaximal Runs

The subject's 30 min submaximal runs (6 mph) were at about 60% of VO_2 max in order to exercise at a point below plasma lactate accumulation (Farrell, Wilmore, Coyle, Billing and Costill, 1979). There were four 30 min submaximal runs involving assessment of RER values and blood parameters: (a) 3 days after the VO_2 max test, (b) 5 days after the VO_2 max test and 1 hour following ingestion of 1 g of nicotinic acid, (c) Day 11 of the nicotinic acid treatment period and 1 hr following the ingestion of 1 g of nicotinic acid, and (d) Day 21 of the nicotinic acid treatment period and 1 hr following the ingestion of 1 g of nicotinic acid. The same treadmill speed (6 mph) was used for each of the four submaximal runs for every subject.

Blood was drawn before and after each 30 min submaximal run for the assessment of serum levels of free fatty acid, glucose, glycerol, and lactate. The RER values were determined using indirect spirometry and were interpreted to reflect carbohydrate and fat utilization. Blood sampling was also used for cholesterol and HDL determination at the beginning and end of the nicotinic acid treatment period.

Nicotinic Acid Treatment

The nicotinic acid treatment period began with a 100 mg dose of nicotinic acid (three times/day). The subjects were asked to take one of the nicotinic acid doses before exercising on their workout days. The nicotinic acid dose increased by 100 mg each day until the subject was up to 1 g three times/day on Day 10. Another 30 min run test was conducted on Day 11 which was followed by 10 days of continued nicotinic acid treatment (3 g/day). Day 21 concluded the subject's participation with

the last 30 min submaximal run test. A three-week nicotinic acid treatment period has proven effective in significantly decreasing plasma cholesterol and raising HDL cholesterol (Shepherd et al., 1979).

Training Log

The subjects were asked to keep a log of outside activity. The training log included date, time of day, type of activity, time exercised, distance covered, and a general rating of perceived exertion (RPE), using the 15 point scale (Borg, 1973) for the workout (Figure 2).

Analysis of Blood Parameters

Blood (15 ml) was drawn from an antecubital vein before and after each of the 30 min submaximal run tests. Analysis included total cholesterol and HDL (only at the start of the experiment and again at the end), and pre- and post-exercise determination of free fatty acid (FFA), glucose, glycerol, and lactate concentrations. The cholesterol assays were done with Sigma kit number 352-20, the glycerol assays were done with Sigma kit number 337, the lactate assays were done with Sigma kit number 826-UV, and the FFA assays were done with Wako kit NEFA C (990-75401). The glucose was analyzed with an Alpkem Autoanalyzer II system using a modification of the Trinder method (Trinder, 1969).

Weekly Training Log

Date	Time	Activity	Exercise Time	Distance	RPE	Comments

Rating of Perceived Exertion (RPE) Scale (Borg, 1973)

6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

Figure 2

Subject's Training Log and RPE Scale

Testing Procedures

After signing the informed consent document and completing medical questionnaires, subjects reported to the laboratory for hydrostatic weighing to determine body composition and an incremental treadmill test to determine VO_2 max. Next the subjects were asked to report to the laboratory 2 and 4 days later at the same time each day (between 0600 and 0900) after a 12 hr fast without engaging in any strenuous exercise during the previous 24 hr period.

Control Features

The subjects served as their own controls because every subject completed each of the four conditions of the independent variable. The testing occurred at the same time of day in order to eliminate any circadian variation and the 12 hr fast serves to minimize the effect of diet on RER. The same individual administered the testing in order to have a more consistent presentation of the testing. Temperature was kept between 20-22°C for all submaximal testing. The duration of data collection was less than 30 days and the subjects were asked not to change their activity routines, so training effects should not have been a factor.

Statistical Analysis

Means and standard deviations were used to compare the subjects for age, height, weight, VO_2 max, and percentage of body fat.

The RER was recorded every minute and then averaged over the last 25 min of the 30 min submaximal run. A repeated-measures analysis of variance (ANOVA)

procedure was used to compare the RER for the four submaximal runs conducted throughout the study. The blood parameters of serum glucose, FFA, glycerol, and lactate levels were also analyzed using separate repeated-measures ANOVA procedures. Total cholesterol and HDL values were compared with a paired t-test.

CHAPTER IV

RESULTS AND DISCUSSION

The intent of this investigation was to examine changes in fuel utilization during and blood-borne substrate levels before and after 30 min of submaximal treadmill running at the beginning, mid-point, and end of three weeks during which pharmacological doses of nicotinic acid were being ingested. Specifically, the fuel utilization was assessed by the respiratory exchange ratio (RER) and the blood-borne substrates included the analysis of serum glucose, glycerol, and free fatty acids (FFA). Lactate levels were also assessed, as were total cholesterol and high density lipoprotein (HDL) cholesterol levels before and after the nicotinic acid treatment period. The organization of the chapter is: (a) results, and (b) discussion.

Results

The results of the study are presented in the following sections: (a) description of subjects, (b) heart rate, oxygen consumption (VO_2), and RER during the submaximal runs, (c) glucose, glycerol, and FFA levels before and after the submaximal runs (d) lactate levels before and after the submaximal runs, and (e) total and HDL cholesterol levels before and after the nicotinic acid treatment period. Raw

data for these variables are provided in Appendix C.

Description of Subjects

Eight 21-41 year old ($\underline{M}$ = 31.2) male subjects participated in the study. The subjects averaged 70.4 inches in height, 153.7 pounds, and 10.3% body fat. The data from the maximal oxygen consumption (VO_2 max) test including maximal values for VO2, heart rate, RER, and rating of perceived exertion (RPE) (Borg, 1973) are presented in Table 3. The training logs indicated that the subjects ran from 3-11 times/week for 25-140 min with an average of 5.2 times/week and 45.5 min per run. The subjects also participated in a small amount of biking, swimming, and weight lifting.

Heart Rate, Oxygen Consumption (VO_2), and RER During the Submaximal Runs

A repeated-measures analysis of variance (ANOVA) procedure was used to compare mean heart rate, mean VO_2, and mean RER, averaged over the last 25 min, during the four submaximal runs conducted over the 21 days of nicotinic acid ingestion. Table 4 contains the means and standard deviations and Table 5 presents the results for the repeated-measures ANOVA for heart rate, VO_2, and RER during the four submaximal treadmill runs. There were no significant differences for mean heart rate or mean VO_2. However, a significant difference ($\underline{p} < .001$) was revealed in the mean RER analysis. Post hoc comparisons, using the Student Neuman Keuls method, indicated that SUB2, SUB3, and SUB4 were significantly higher than SUB1 and SUB2 was also significantly higher than SUB3 and SUB4. (Figure 3).

Table 3

Results of the $\dot{V}O_2$ max Test

Subject	$\dot{V}O_2$ max ($ml \cdot kg^{-1} \cdot min^{-1}$)	HR max ($b \cdot min^{-1}$)	RER max	RPE max	Age
1	72.4	192	1.19	18	21
2	62.0	188	1.13	19	33
3	56.4	195	1.20	19	28
4	62.7	178	1.06	20	39
5	54.4	175	1.17	18	36
6	60.2	180	1.06	19	26
7	63.7	167	1.04	17	41
8	54.7	210	1.12	20	26
M	60.8	185.6	1.12	18.75	31.25
SD	5.52	12.64	.059	.968	6.63

Table 4

Means and Standard Deviations for Heart Rate (HR), VO_2, and RER

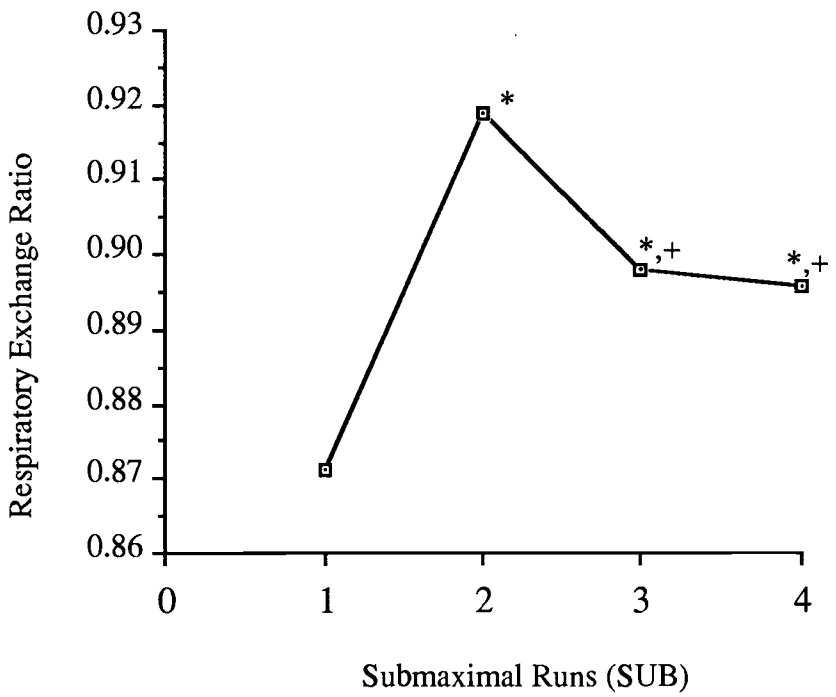
Submaximal Runs	1	2	3	4
HR (beats·min^{-1}	130.0 (14.670)	132.8 (18.296)	132.8 (12.606)	129.9 (11.350)
$\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	36.4 (2.854)	35.1 (2.930)	36.5 (3.361)	36.0 (2.405)
RER	.8712 (.2010)	.9187 (.0233)	.8980 (.0188)	.8959 (.0229)

Table 5

Repeated-Measures ANOVA Results for HR, VO_2, and RER

	F	p
HR (beats·min^{-1}	.603	.620
$\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	2.752	.068
RER	9.119	.001*

* Indicates significant difference ($p < .05$)



* value significantly different from SUB1 value, $p < .05$
+ value significantly different from SUB2 value, $p < .05$

Figure 3

RER for SUB1 (without nicotinic acid) and SUB2, SUB3, and SUB4 (with nicotinic acid ingestion 1 hr prior to runs at 1, 11, and 21 days of nicotinic acid treatment)

Glucose, Glycerol, and FFA Levels Before and After the Submaximal Runs

A repeated-measures ANOVA procedure was used to compare mean pre- and mean post-submaximal run levels in addition to mean delta scores for glucose, glycerol, and FFA. Table 6 reports the means for glucose, glycerol, and FFA before and after each of the submaximal runs. Table 6 also shows the means for the delta scores that were computed by subtracting the pre values from the post values. Table 7 contains the results for the repeated-measures ANOVAs for mean glucose, mean glycerol, and mean FFA data. There were no significant differences reported in the mean pre-run and mean delta values for glucose. The mean post-run values for glucose were significantly different ($p < .05$), although post hoc analyses did not detect differences. The mean post-run and mean delta glycerol values were both significantly different ($p < .001$) across the four SUBs with no change detected in pre-run values. The post hoc comparisons indicated that mean post and mean delta glycerol values for SUB1 were significantly different ($p < .05$) from the other submaximal runs. The mean pre, post, and delta values for FFA were all significantly different ($p < .001$) across the four submaximal runs. The post hoc analyses revealed that SUB1 was significantly different ($p < .05$) from the rest of the SUBs in all of the FFA values. The Figures 4, 5, and 6 contain the mean values for the delta scores for glucose, glycerol, and FFA, respectively.

Table 6

Means and Standard Deviations for Glucose (Glu), Glycerol (Gly), and FFA for Pre- and Post- Submaximal Runs and Delta Values

Submaximal Runs	1	2	3	4
Glu ($mg \cdot dl^{-1}$)				
Pre	79.53	83.04	86.92	85.44
	(4.62)	(9.30)	(9.45)	(10.2)
Post	91.87	90.31	102.19*	93.12
	(5.42)	(4.00)	(10.26)	(9.22)
Delta	12.33	7.27	15.27	7.69
	(5.35)	(7.88)	(7.90)	(4.36)
Gly ($mg \cdot dl^{-1}$)				
Pre	3.19	1.61	2.11	2.77
	(1.11)	(.679)	(1.14)	(2.28)
Post	12.97*	3.05	4.88	6.13
	(2.89)	(2.23)	(2.15)	(2.62)
Delta	9.78*	1.45	2.76	3.36
	(3.27)	(1.93)	(1.47)	(2.91)
FFA ($mEq \cdot l^{-1}$)				
Pre	0.456*	0.124	0.227	0.123
	(.209)	(.035)	(.143)	(.036)
Post	0.759*	0.070	0.091	0.129
	(.182)	(.034)	(.043)	(.061)
Delta	0.303*	-0.055	-0.137	0.006
	(.177)	(.041)	(.144)	(.039)

* Indicates significant difference in post hoc comparisons compared to the other three SUBs ($p < .05$)

Table 7

Repeated-Measures ANOVA Results for Pre- and Post-Submaximal Runs and Delta Values for Glucose, Glycerol, and FFA

		F	p
Glucose ($mg \cdot dl^{-1}$)			
	Pre	2.118	.128
	Post	10.480	.001*
	Delta	3.990	.021*
Glycerol ($mg \cdot dl^{-1}$)			
	Pre	2.428	.094
	Post	36.239	.001*
	Delta	23.675	.001*
FFA ($mEq \cdot l^{-1}$)			
	Pre	12.603	.001*
	Post	84.033	.001*
	Delta	17.625	.001*

* Indicates significant difference ($p < .05$)

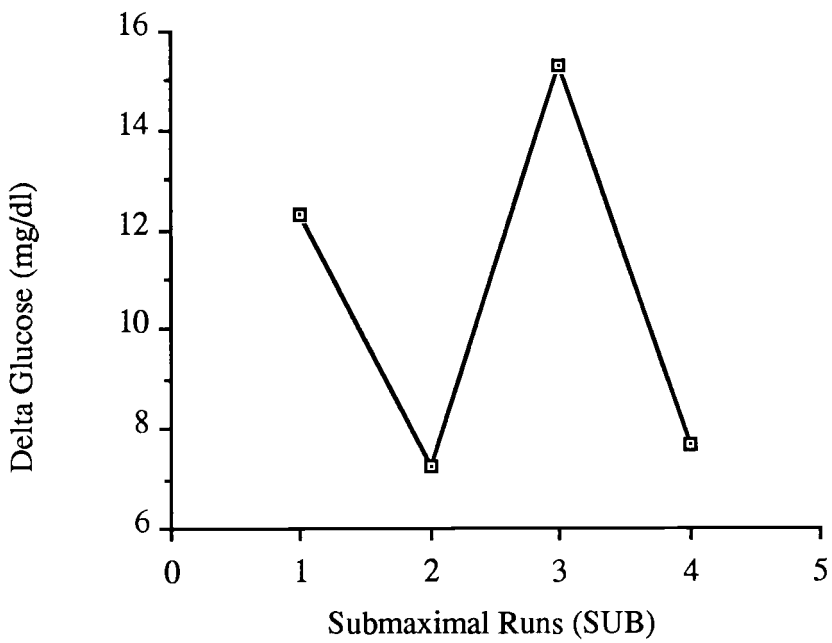
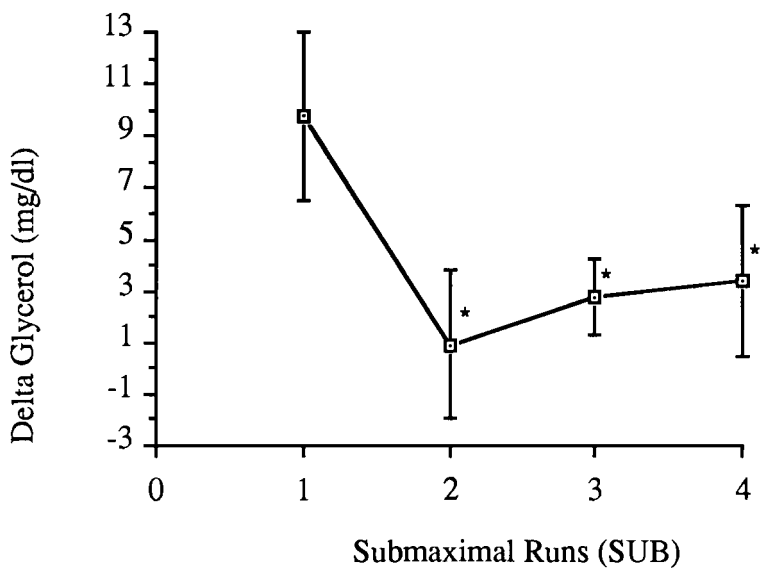


Figure 4

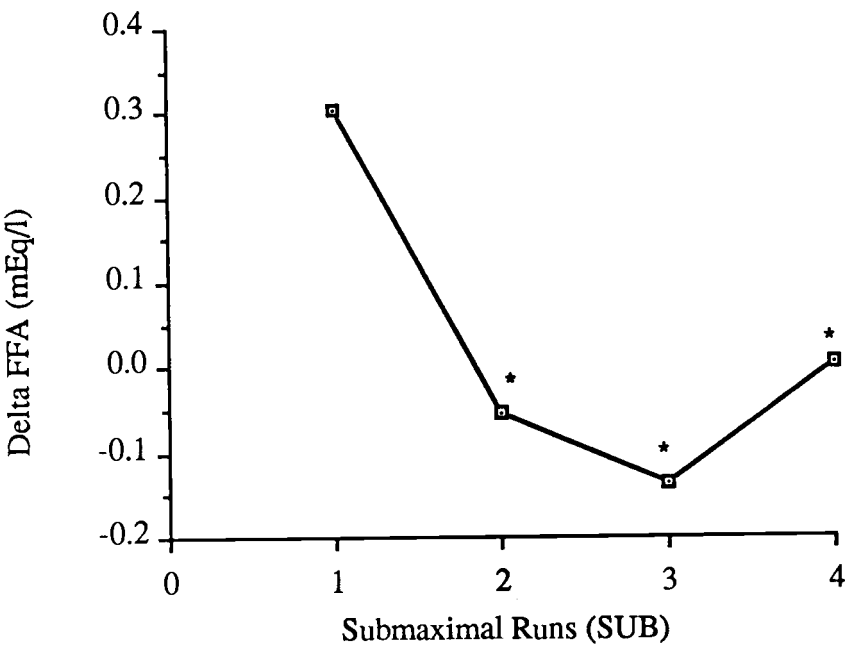
Delta Glucose Values for the Four Submaximal Runs



* value significantly different from SUB1 value, $p < .05$

Figure 5

Delta Glycerol Values for the Four Submaximal Runs



* value significantly different from SUB1 value, $p < .05$

Figure 6

Delta FFA Values for the Four Submaximal Runs

Lactate Levels Before and After the Submaximal Runs

A repeated-measures ANOVA indicated that there were no significant differences in the mean delta values (post - pre) for lactate levels before and after the submaximal runs ($F = 1.765$, $p = .185$). The mean values before the SUBs were .85 $mg \cdot dl^{-1}$ and the means for after the SUBs were 1.64 $mg \cdot dl^{-1}$.

Total and HDL Cholesterol Levels Before and After the Nicotinic Acid Treatment

The Student's paired t statistic was used to compare total and HDL cholesterol levels before and after the nicotinic acid treatment period. Table 8 presents the means and standard deviations for both total and HDL cholesterol. Table 9, the results of the Student's t test, indicates that there were significant differences ($p < .05$) to report for total and HDL cholesterol as a result of the nicotinic acid treatment. The total cholesterol decreased and the HDL cholesterol increased, as shown in Figure 7.

Table 8

Means and Standard Deviations for Total (Chol) and HDL Cholesterol Before and After Nicotinic Acid Treatment

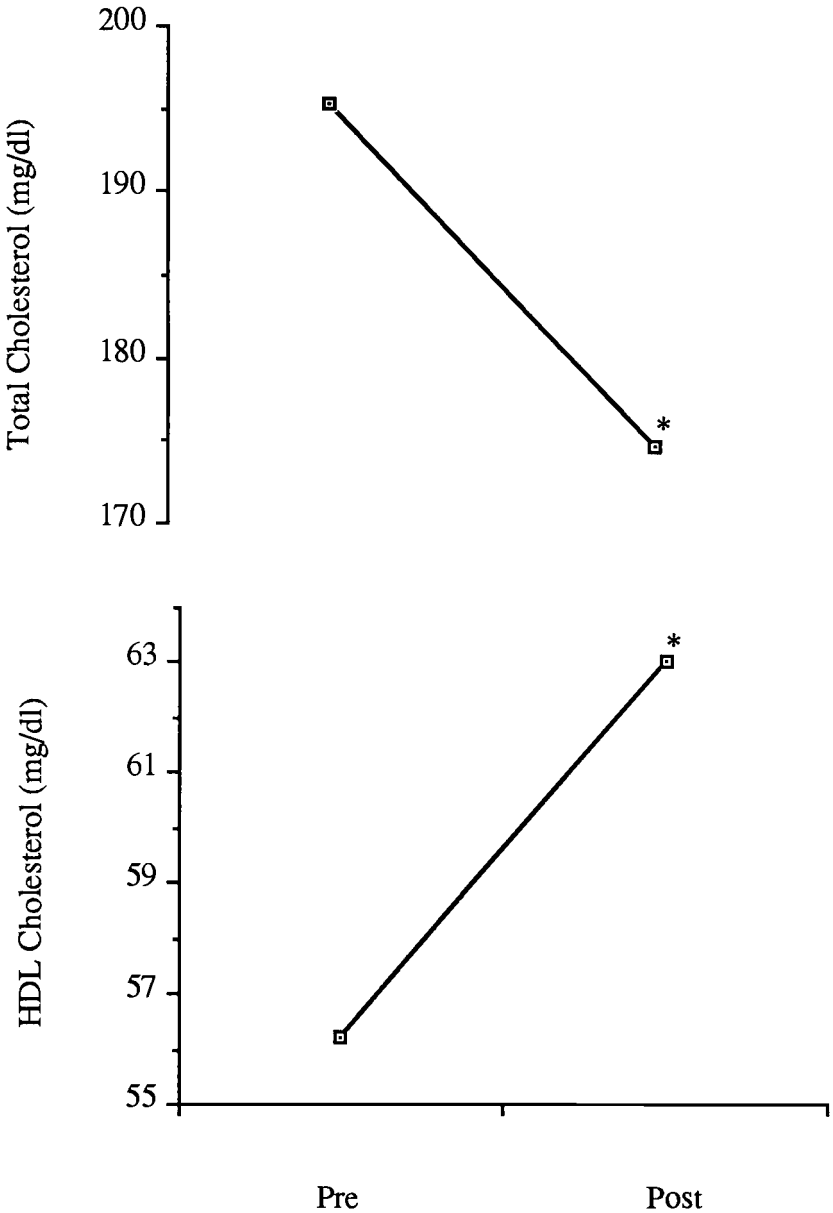
	Pre	Post
Chol ($mg \cdot dl^{-1}$)	195.26 (24.34)	174.51 (24.31)
HDL ($mg \cdot dl^{-1}$)	56.22 (7.80)	63.04 (10.42)

Table 9

Computed t Statistic Results for Total (Chol) and HDL Cholesterol Before and After Nicotinic Acid Treatment

	F	p
Chol ($mg \cdot dl^{-1}$)	6.734	.036*
HDL ($mg \cdot dl^{-1}$)	8.686	.021*

* Indicates a significant difference ($p < .05$)



* value significantly different from pre value, $p < .05$

Figure 7

Total and HDL Cholesterol

Discussion

The discussion of the results is presented under the following headings: (a) heart rate and VO_2 during the submaximal runs, (b) glucose, glycerol, and FFA levels before and after and RER during the submaximal runs, (c) lactate levels before and after the submaximal runs (d) total and HDL cholesterol before and after the nicotinic treatment period, and (d) summary.

Heart Rate and VO_2 During the Submaximal Runs

There were no differences observed in either heart rate or VO_2 over the course of the four submaximal runs. The average heart rate ranged from a low of 129.9 beats·min^{-1} for SUB4 to a high of 132.8 beats·min^{-1} for SUB2 and SUB3 (Table 4). The average $\dot{V}O_2$ ranged from a low of 35.1 $\pm$ 2.93 (SD) ml·kg^{-1}·min^{-1} for SUB2 to a high of 36.5 $\pm$ 3.36 ml·kg^{-1}·min^{-1} for SUB3 (Table 4). The subjects had relatively high $\dot{V}O_2$ max values ($\underline{M}$ = 60.8 $\pm$ 5.52 ml·kg^{-1}·min^{-1}) and were asked to maintain the regular training schedule so no changes were expected in heart rate and VO_2 over the four submaximal runs.

The results concur with Carlson et al. (1963), who report no change in exercise heart rate or oxygen consumption with nicotinic acid administration, whereas Bergström and co-workers (1969) reported a significant increase in exercise heart rate and oxygen consumption with nicotinic acid administration. Bergström et al. (1969) most likely reported spurious results because of not considering the order effect in their study's design. All of the 15 subjects in the Bergstrom study completed an

exercise session immediately prior to the administration of nicotinic acid and subsequent exercise. Thus, the heart rates and VO_2 responses reported could have been elevated as a result of the previous exercise session. Jenkins (1965), as did Carlson (1963), reported no differences in VO_2 as a result of nicotinic acid administration.

Glucose, Glycerol, and FFA Levels Before and After and RER During the Submaximal Runs

The variables discussed in this section are factors in determining fuel utilization. Previous research determined that the acute administration of nicotinic acid caused a decrease in fat utilization during exercise (Carlson et al., 1963; Jenkins, 1965). The evidence to suggest what happens to these variables in a prolonged nicotinic acid treatment period has been lacking, prior to the present study.

RER

The RER, an indirect method of determining substrate utilization, was significantly different across the four submaximal runs. An increase in the RER is an indication of a decreased contribution of energy derived from lipid sources. Post hoc analysis showed that the RER rose significantly from SUB1 to SUB2 (.871 to .918) and then decreased significantly on SUB3 and remained the same for SUB4 (.898 and .896), although still significantly above SUB1 levels (Table 4 and Figure 3). The RER for SUB1 (.871) represented approximately 57.5 percent of the kcal derived from carbohydrate and approximately 42.5 percent of the kcal derived from fat; SUB2 RER (.918) represented 74.1% from carbohydrate sources and 25.9% from fat

sources; SUB3 RER (.898) and SUB4 RER (.896) represented 67.5% from carbohydrate sources and 32.5% from fat sources (McArdle, Katch and Katch, 1986). The RER data indicates that the initial nicotinic acid dose (SUB2) significantly reduced fat utilization and the pattern was continued as the three week nicotinic acid treatment period progressed resulting in a persistent, although lessened inhibition during subsequent submaximal runs (SUB3 and SUB4). Previous research has reported this same reduction in fat utilization, or increased RER, in single bouts of exercise with prior administration of nicotinic acid. Jenkins (1965) reported that the RER increased from .867 (without prior nicotinic acid) to .916 (with prior nicotinic acid), which are very similar to the results reported in this investigation. Carlson et al. (1963) also demonstrated increased RER values in exercise with prior administration of nicotinic acid.

The decrease in fat utilization with nicotinic acid administration was demonstrated in previous research, although the adaptation to less inhibited fat utilization as nicotinic acid treatment continued, evident in SUB3 and SUB4, is a new finding. In a similar type of treatment, there has not been evidence to show that extended use of beta-blockers results in metabolic adaptations. Beta-blockers decrease serum FFA and long term use has not shown any attenuation in this response (Frisk-Holmberg, Jorfelt, Juhlin-Dannfelt and Karlsson, 1979). In contrast, the results of this study would suggest a metabolic adaptation to the chronic use of nicotinic acid. The mechanism of the adaptation could involve the effect of nicotinic acid on the level of cyclic AMP. With acute nicotinic acid administration, adenylcyclase is inhibited,

which causes a reduction in the concentration of cyclic AMP, which in turn interferes with the activation of hormone sensitive lipase (Madsen and Malchow-Moller, 1983). Thus, the result is a decreased breakdown of adipose tissue triglycerides to glycerol and FFA to serve as an energy substrate. The adaptation to chronic nicotinic acid administration could involve a decreased sensitivity of the inhibition of adenylcyclase by nicotinic acid or perhaps a lessened effect on decreasing the action of hormone sensitive lipase.

Glucose

Pre-run glucose values were not significantly different during the course of the study. The pre-run glucose values demonstrated some variability, although the pattern was not statistically significant. The post-run glucose values were significantly higher at SUB3 (Table 6), although the change was not enough to achieve significance in the delta glucose values.

In trained individuals, blood glucose does not change much under normal circumstances in mild to moderate exercise lasting for less than one hour. Blood glucose levels may actually increase for a time during exercise as a result of accelerated release of glucose from the liver. If the exercise increases to 70% of VO_2 max, the glucose levels are expected to fall slightly during an hour exercise session (Åstrand, 1986; Brooks and Fahey, 1984).

The slight, although not significant, increase in pre-run glucose levels found in this study is similar to the resting data of Martineau and Jacobs (1989). Although there was a small increase in glucose levels, Martineau and Jacobs (1989) reported

that glucose concentrations were similar with and without nicotinic acid ingestion in a two hour rest period.

The expected rise in glucose at the end of the 30 min runs was not seen until the tenth day of the nicotinic acid ingestion period. This significant rise in the post-exercise value was not of sufficient magnitude to produce significant changes in the delta values. Earlier researchers only examined the effects of nicotinic acid on an isolated bout of exercise, so the increased post-run glucose concentration seen at Day 11 of the nicotinic acid treatment is a new finding. Carlson and others (1963) demonstrated a slight decrease for the first 30 min of exercise with previous nicotinic acid ingestion. The investigation of Jenkins (1965) and Bergström et al. (1969) are not comparable to the present one. After 60 min of exercise, Jenkins (1965) reported that glucose values decreased significantly with prior nicotinic acid ingestion, although the glucose values were significantly higher than control subjects (without nicotinic acid). The research of Bergström and co-authors (1969) cannot be compared because of the problem of the order effect discussed earlier.

The increase in glucose concentration seen in Day 11 of the nicotinic acid treatment appears to be an adaptation to the chronic nicotinic acid dose. The shift toward increased carbohydrate metabolism is apparent after 11 days of nicotinic acid administration.

Glycerol

Pre-run glycerol values demonstrated downward (SUB1 to SUB2) and then upward (SUB2 to SUB3 to SUB4) trends with repeated nicotinic acid ingestion (Table

6). As expected, post-run and delta glycerol values were significantly higher in the submaximal run without prior nicotinic acid ingestion. The expected adaptation (return to normal fat utilization during the nicotinic acid treatment period) was not exhibited in the post-run and delta glycerol values for Day 11 and 21. The post-run and delta glycerol values were lowest at SUB2 of the nicotinic acid treatment and increased for SUB3 and SUB4, although the changes were not statistically significant compared to SUB2.

Martineau and Jacobs (1989) reported that resting glycerol concentrations were significantly depressed with prior administration of nicotinic acid. The present study did not show any significant difference in the pre-run glycerol values. This discrepancy in resting glycerol levels could have been a function of procedural differences. Martineau and Jacobs (1989) took blood samples every 30 min after the first nicotinic acid ingestion for a total of two hours, whereas in the present study, only one sample was taken (one hour after nicotinic acid ingestion). Martineau and Jacobs (1989) also had continued nicotinic acid ingestion every half hour of 1.6 $mg \cdot kg^{-1}$ after the initial dose of 3.2 $mg \cdot kg^{-1}$. The resting glycerol values did not change with prior administration of nicotinic acid in the study of Carlson et al. (1963), and Jenkins (1965) did not report glycerol levels.

The post-run and delta glycerol values in SUB2, SUB3, and SUB4 were significantly lower than SUB1 (without nicotinic acid ingestion). Carlson and co-authors (1963) reported a similar pattern of inhibition of glycerol levels during exercise with prior nicotinic acid administration.

The inhibition of the breakdown of white adipose tissue triglycerides to glycerol and FFA caused by nicotinic acid's action on adenylcyclase and hormone sensitive lipase was apparent in the glycerol data. There was no adaptation in the glycerol levels with the three weeks of nicotinic acid treatment, only a slight, nonsignificant rise in the delta glycerol values.

FFA

All three FFA values (pre, post, and delta) were significantly elevated in the submaximal run without nicotinic acid administration (SUB1) (Table 6). Similar results are reported in all previous research on the effect of nicotinic acid ingestion on bouts of exercise. The inhibited release of FFA with nicotinic acid ingestion both at rest and exercise was evident in every study reviewed.

Martineau and Jacobs (1989) reported that FFA concentrations were dramatically reduced by nicotinic acid ingestion, averaging .087 $\pm$ .015 $mmol \cdot l^{-1}$ at the end of two hours of rest. Carlson et al. (1963) indicated that nicotinic acid administration significantly reduced the concentration and turnover rate of FFA at rest.

Jenkins (1965) reported significant differences in FFA concentrations during exercise in controls compared to subjects who ingested nicotinic acid. The control subjects demonstrated the normal rise in FFA levels, whereas the subjects who ingested nicotinic acid experienced an inhibition of that rise in FFA levels. Carlson et al. (1963) demonstrated a similar inhibition of FFA elevation during exercise with prior ingestion of nicotinic acid.

The FFA levels were suppressed during the nicotinic acid treatment owing to nicotinic acid's inhibition of the release of FFA and glycerol from adipose tissue. Although there was no adaptation seen in the delta FFA levels over the three weeks of nicotinic acid treatment, the delta FFA values showed a nonsignificant increase from SUB2 to SUB4.

Lactate Levels Before and After the Submaximal Runs

As expected, the lactate levels before and after the submaximal runs did not demonstrate any significant differences. If lactate levels increased in the post sample, it would have indicated that expired CO_2 was not entirely from metabolism and the RER values would not have been an accurate reflection of fuel utilization. Trained runners exercising at 60-65% of their VO_2 max are not expected to accumulate lactic acid (Farrell et al., 1979).

Total and HDL Cholesterol Before and After the Nicotinic Acid Treatment Period

The total cholesterol was significantly lower and the HDL cholesterol was significantly higher after the three weeks of nicotinic acid treatment (Table 8). Many researchers have reported similar results (Alderman et al., 1989; Atmeh et al., 1983; Blankenhorn et al., 1987; The Coronary Drug Project Research Group, 1975; Gluek, 1985; Gurakar, 1985; Hanefeld et al., 1984; Kane et al., 1981; Shepherd et al., 1979). The difference is that almost all of these studies involved older subjects who had symptoms or signs of coronary artery disease.

Shepherd and co-workers (1979) conducted a study similar to the present one except that there was no indication that the subjects were highly fit, habitual exercisers. However, the subjects were healthy and young (aged 23-29 years) and the nicotinic acid dose was 3 g/day for three weeks, as in the present. The total cholesterol values were significantly reduced (163 $\pm$ 9 to 139 $\pm$ 16 $mg \cdot dl^{-1}$) and the HDL values were significantly increased (52 $\pm$ 12 to 64 $\pm$ 12 $g \cdot dl^{-1}$). The change values are very similar to the ones in this study.

Summary

The changes in fuel utilization over the course of the three week period of nicotinic acid ingestion was the most important aspect of this investigation. The RER values demonstrated a significant increase from SUB1 (.871) to SUB2 (.919) and then a significant decrease from SUB2 to SUB3 (.898) and SUB4 (.896) (which was still significantly higher than SUB1). The nicotinic acid dose (SUB2) significantly decreased fat utilization from pre-treatment values (SUB1) and showed an adaptation toward a slightly greater rate of fat utilization at Day 11 (SUB3) and Day 21 (SUB4). The RER values showed a significant adaptation to the nicotinic acid as fat utilization was less suppressed in Days 11 and 21 of testing. The delta values for glycerol and FFA were significantly decreased in SUB2, SUB3, and SUB4, indicating a reduction in fat utilization during the nicotinic acid treatment period. The blood glycerol and FFA data were similar for SUB2, SUB3, and SUB4, indicating no adaptation to the nicotinic acid treatment. The speculation on the mechanism of the adaptation to chronic nicotinic acid treatment seen in the RER values is somewhat confused by the

continued suppression of the fat substrates, glycerol and FFA. The expectation would be that if there is a decreased sensitivity of the inhibition of adenylcyclase or a lessened effect on decreasing the action of hormone sensitive lipase by nicotinic acid, then there should be increasing levels of serum glycerol and FFA. But the glycerol and FFA data does not demonstrate any adaptation in SUB3 and SUB4. Thus, the mechanism may involve something completely different, such as increased utilization of intramuscular triglyceride in response to the continued reduced availability of serum FFA.

An interesting finding of the research was that total cholesterol was significantly reduced and HDL cholesterol was significantly increased after the three week period of nicotinic acid treatment.

CHAPTER V

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Summary

The purpose of this study was to examine the changes in fuel utilization during and blood-borne substrate levels before and after 30 min of submaximal treadmill running at the beginning, mid-point, and end of a three week treatment period during which pharmacological doses of nicotinic acid were administered. The subjects for this investigation were eight males with a mean age of 31.2 $\pm$ 6.6 (SD) years; height of 70.4 $\pm$ 2.0 inches; weight of 153.7 $\pm$ 19.3 pounds. They were trained, habitual runners ($\dot{V}O_2$ max of 60.8 $\pm$ 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$) who ran an average of 5.2 times/week and 45.5 min per run.

After the collection of descriptive data, the subjects reported to the laboratory, following a 12-14 hour overnight fast, for their first of four 30 min submaximal runs (6 mph). The second submaximal run was performed one hour after the ingestion of a 1 g dose of nicotinic acid. Twenty-one days of nicotinic acid ingestion (starting with 100 mg taken three times/day) followed. The nicotinic acid dose was taken three times/day and the dose was increased by 100 mg/day during days 2-10, at which time the subjects reached the target dose of 1 g taken three times/day. On Day 11 the

subjects performed the third submaximal run. The target dose of 3 g/day continued until Day 21 when the last 30 min submaximal run was conducted. Heart rate, VO_2, and RER data were collected during the submaximal runs. Blood was drawn before and after the submaximal runs to analyze serum levels of glucose, glycerol, free fatty acid, and lactate. Sampled blood was also used for determination of total and HDL cholesterol at the beginning and end of the nicotinic acid treatment period.

Repeated-measures ANOVA procedures were used to compare heart rate, VO_2, and RER, averaged over the last 25 min, during the four submaximal runs (SUB). Although there were no differences in heart rate or VO_2, RER demonstrated significant differences between the four submaximal runs (RER: SUB1, .871; SUB2, .919; SUB3, .898; SUB4, .896). Post hoc comparisons revealed that SUB2, SUB3, and SUB4 values were significantly greater than the SUB1 RER, and that the SUB2 RER was also significantly greater than SUB3 and SUB4, which did not differ from each other. The initial dose significantly reduced fat utilization and continued nicotinic acid treatment resulted in a persistent, though lessened inhibition during subsequent runs.

Repeated-measures ANOVA procedures were also used to compare pre- and post-submaximal run levels in addition to delta scores for glucose, glycerol, and FFA. There were no significant differences reported in the pre-run and delta values for glucose across the four SUBs. The post-run values for glucose were significantly different ($p < .05$) across the four SUBs, although post hoc analyses did not detect where the differences were. The post and delta glycerol values were both significantly

different ($p < .001$) across the four SUBs with no change detected in pre-run values. The post hoc comparisons indicated that post- and delta-glycerol values for SUB1 were significantly different ($p < .05$) from the other submaximal runs. The pre, post, and delta values for FFA were all significantly different ($p < .001$) throughout the four submaximal runs. The post hoc analyses revealed that SUB1 was significantly different ($p < .05$) from the other SUBs.

The Student's t statistic was used to compare pre- and post-treatment total and HDL cholesterol. Significant decreases in total cholesterol and significant increases in HDL cholesterol occurred during the treatment period.

Nicotinic acid treatment caused significant decreases in fat utilization and the RER data demonstrated an adaptation to chronic ingestion of nicotinic acid where the blood-borne substrates did not. The cholesterol levels were significantly affected by nicotinic acid treatment, showing a decrease in total cholesterol and an elevation in HDL cholesterol.

Conclusions

Given the design of this study, the following conclusions can be made:

1. Fuel utilization shifted to greater carbohydrate metabolism with nicotinic acid administration and then started to return to baseline values with continued nicotinic acid administration. Nicotinic acid treatment resulted in RER values for SUB2, SUB3, and SUB4 that were significantly higher than SUB1, and SUB2 RER values were also significantly higher than SUB3 and SUB4.

2. Circulating levels of glycerol and FFA were lower with nicotinic acid administration and did not adapt to chronic nicotinic acid administration. Glycerol and FFA delta values were significantly lower in SUB2, SUB3, and SUB4 as compared to SUB1. And there were no statistically significant differences among the SUB2, SUB3, and SUB4 values.
3. Delta glucose values were unchanged throughout the four submaximal runs, indicated that the availability and/or utilization of blood glucose was unchanged by the nicotinic acid treatment.
4. Delta lactate values did not change throughout the four submaximal runs, indicating that the nicotinic acid treatment did not affect the balance between lactate release and uptake.
5. Total cholesterol levels were significantly reduced after the nicotinic acid treatment period.
6. Levels of HDL cholesterol were significantly increased after the nicotinic acid treatment period.

Recommendations

The following recommendations are suggested for future research:

1. To continue the nicotinic acid treatment period beyond the three weeks to determine if the trend toward a return to normal fat utilization is realized.

2. Select an older or diseased group of subjects that is more likely to be prescribed nicotinic acid for controlling cholesterol.
3. Investigate the interaction between nicotinic acid ingestion and exercise by selecting two groups with no previous regular exercise experience and train them (with and without nicotinic acid treatment) and two groups that remain sedentary (with and without nicotinic acid treatment).

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APPENDICES

APPENDIX A

STATEMENT OF INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

CONSENT FORM

Title: Effects of nicotinic acid treatment on substrate utilization, cholesterol, free fatty acid, and glucose during submaximal exercise

Investigators: Edward M. Heath, Anthony R. Wilcox, Ph.D.

Purpose: Previous studies have investigated the effects of nicotinic acid (NA) ingestion on changes in substrate utilization (fuel source for the body) during acute exercise. The present study will investigate the effects of NA ingestion (building up to 3 g per day -- 1 g 3 times per day) on substrate utilization during four 30 min submaximal treadmill runs over 24 days. The study will also investigate the changes in cholesterol, free fatty acid (FFA) and glucose levels during the submaximal runs throughout the 24 days.

I have received an oral explanation of the study procedures and understand that they entail:

1. **A test of maximal oxygen consumption on a motor-driven treadmill.** The test will begin at an easy speed (6 mph) and 0% grade for a 4 min warm-up period. After the 4 min, the speed will increase 1 mph at 2 minute intervals until reaching a speed of 9 mph. Then the slope will be increased 2% every 2 minute thereafter until I become too fatigued to continue. The test usually takes 10-15 minutes, with only the final few minutes being at a high intensity. I will be breathing through a mouthpiece so that the amount of oxygen my body is using during the exercise test can be determined.

2. **A test of body composition using hydrostatic weighing.** Underwater weight will be determined by submerging, after a maximal exhalation, while sitting on a PVC pipe platform suspended from a load cell. Along with the assessment of residual volume (volume of air left in the lungs after a maximal expiration, the underwater weight will be used to calculate percent body fat using prediction formulas.

3. **Nicotinic acid (NA) treatment procedure.** Before the last three submaximal treadmill runs, I will ingest 1 g of NA (2 small pills) one hour prior to the run. The NA treatment will begin with a 100 mg dose of NA (three times per day). I will take one of the NA doses before exercising on workout days. The NA doses will increase 100 mg each day until the dose is up to 1 g three times per day on Day 10. Another 30 minute run test will be conducted on Day 11 which will be followed by 10 days of continued NA treatment (3 g per day).

4. **A test of substrate utilization (assessed by collection of expired air) and blood-borne substrate levels during submaximal treadmill running.** There will be four 30 minute submaximal treadmill runs: (1) before NA treatment, (2) after ingestion of 1 g NA, (3) Day 11 of NA treatment , and (4) Day 21 of NA treatment. I will run on a level motor-driven treadmill at 65% of maximal oxygen consumption (speed determined from max test) for 30 minutes while breathing through a mouthpiece for gas analysis purposes. A blood sample of 10-15 ml will be taken from an antecubital vein before and after the run for analysis of blood-borne substrate levels.

5. **Recording of an activity log.** I will keep an activity log that includes date, time of day, type of activity, time exercised, distance covered, and a general rating of exertion level.

I understand that the test of maximal oxygen consumption has a very remote chance of precipitating a cardiac event (such as abnormal heart rhythms) or even death. However, the possibility of such an occurrence is very slight (less than 1 in 10,000), since I am in good physical condition with no known symptoms of heart disease, and since the test will be administered by trained personnel who will be monitoring electrocardiographic and other physiologic responses to the test.

I am aware that there is a chance I may experience side effects of NA ingestion. The most common side effect is flushing, a reddening of the skin with an itching sensation. The gradual increase in the NA dose will decrease the chance of the appearance of this flushing symptom and the symptom should disappear with repeated administration of NA. Flushing can also be reduced with: (1) ingestion of NA with a meal, and (2) prior administration of aspirin. Chances of other side effects are minimal since I am in good health.

The benefits of my participation in the study include contributing to the scientific study of substrate utilization and levels of blood-borne substrate during submaximal running and the knowledge I will gain concerning my aerobic capacity and body composition.

I understand that my participation in the project will entail five laboratory sessions, with each visit requiring from 45 to 60 minutes.

I understand that my anonymity will be maintained by codifying my data files. Upon entry into the study, I shall receive a code number to identify my data and all records shall be kept using the code number.

I have been completely informed and understand the nature and purpose of this research. The researchers have offered to answer any further questions that I may have. I understand that my participation in this study is completely voluntary and I

may withdraw from the study at any time without prejudice or loss of the benefits to which my participation entitles me.
If I experience any discomfort of injury during the course of my participation in this research project, I am to call Dr. Anthony R. Wilcox at 737-2631 or Edward M. Heath at 737-3221.

I have read the foregoing and agree to participate in this study.

_____ _____
Subject's Signature Date

_____
Subject's Address

_____ _____
Investigator's Signature Date

APPENDIX B

MEDICAL QUESTIONNAIRE

MEDICAL QUESTIONNAIRE

Name_____ Address_____

_____

Age_____ Phone_____

Height_____ Weight_____ Gender_____

Circle the appropriate responses:

1) Do you smoke cigarettes?

yes no

2) If yes, have you smoked cigarettes regularly in the last 5 years?

yes no

3) Have you ever been treated for high blood pressure?

never in a physician's office in the hospital

4) Have you ever been treated for "sugar diabetes" (diabetes mellitus)?

never with pills with insulin injections

5) Did either of your parents have a "heart attack" or bypass surgery?

do not know neither one both

If yes, were they: under age 50 50 years or over

6) Have you ever had an elevated blood cholesterol level?

do not know no yes

7) Do you know your blood cholesterol level?

Yes _____mg/100 ml blood no

8) Describe your exercise habits.

9) Do you have infectious mononucleosis?

yes no

10) Do you have or have you had a peptic ulcer?

yes no

11) Do you have or have you had gout?

yes no

12) Do you or have you had hepatitis? (symptoms may include nausea, vommitting, loss of appetite, yellowish skin, fever and itching)

yes no

13) What would you estimate your alcohol consumption to be?

none less than 1 beer (or equivalent) per day

less than 3 beers per day less than 6 beers per day

greater than 6 beers per day

14) Are you taking any prescription medications? If yes, please list kind and amount.

APPENDIX C

RAW DATA

$\dot{V}O_2$, Respiratory Exchange Ratio, and Heart Rate

Subject	SUB	$\dot{V}O_2$	RER	HR
1	1	35.010	0.850	125.330
1	2	35.950	0.894	132.000
1	3	38.944	0.870	134.667
1	4	37.946	0.884	135.833
2	1	36.760	0.868	126.170
2	2	36.146	0.964	127.333
2	3	38.313	0.908	136.170
2	4	36.846	0.944	135.833
3	1	38.968	0.868	134.000
3	2	38.601	0.920	148.000
3	3	39.724	0.931	147.000
3	4	37.565	0.898	134.830
4	1	36.406	0.852	121.167
4	2	34.362	0.887	118.833
4	3	35.118	0.876	114.830
4	4	34.392	0.906	114.833
5	1	31.780	0.882	114.167
5	2	30.286	0.901	114.000
5	3	32.109	0.884	118.167
5	4	32.431	0.883	117.833
6	1	41.324	0.893	145.333
6	2	39.082	0.936	143.333
6	3	41.344	0.902	145.167
6	4	40.107	0.900	133.333

7	1	33.316	0.847	114.667
7	2	31.224	0.922	110.833
7	3	31.976	0.904	119.667
7	4	33.367	0.858	118.000
8	1	37.590	0.910	159.500
8	2	35.144	0.926	168.500
8	3	34.127	0.909	146.667
8	4	35.550	0.894	148.700

Glucose

Subject	SUB	Pre	Post	Delta
1	1	77.64	88.84	11.2
1	2	92.63	89.39	-3.24
1	3	90.85	98.92	8.07
1	4	78.66	89.07	10.41
2	1	80.81	99.69	18.88
2	2	82.5	94.96	12.46
2	3	89.9	117.62	27.72
2	4	98.33	104.07	5.74
3	1	76.31	92.43	16.12
3	2	81.29	90.63	9.34
3	3	84.68	99.29	14.61
3	4	85.19	89.68	4.49
4	1	90.24	92.75	2.44
4	2	92.55	94.52	1.97
4	3	107.25	113.32	6.07
4	4	100.09	106.72	6.63
5	1	75.51	85.33	9.82
5	2	68.9	81.5	12.6
5	3	71.36	85.77	14.41
5	4	66.83	79.67	12.84
6	1	81.97	100.72	18.75
6	2	69.37	88.97	19.6
6	3	83.57	110.8	27.23
6	4	90.14	101.77	11.63

7	1	78.36	85.94	7.58
7	2	83.04	93.03	10
7	3	84.09	91.52	7.43
7	4	79.05	89.9	10.85
8	1	75.38	89.23	13.85
8	2	94	89.46	-4.54
8	3	83.63	100.27	16.64
8	4	85.21	84.11	-1.1

Glycerol

Subject	SUB	Pre	Post	Delta
1	1	3.811	8.362	4.551
1	2	0.398	0.341	-0.057
1	3	1.536	1.82	0.284
1	4	0.967	0.683	-0.284
2	1	2.225	11.498	9.273
2	2	2.225	1.484	-0.741
2	3	2.225	7.418	5.193
2	4	1.855	4.08	2.225
3	1	2.684	14.417	11.733
3	2	1.074	2.607	1.533
3	3	0.846	4.524	3.678
3	4	1.15	9.739	8.589
4	1	5.354	14.178	8.824
4	2	1.659	2.79	1.131
4	3	4.072	7.903	3.831
4	4	8.522	7.419	-1.103
5	1	2.258	17.5	15.242
5	2	2.097	5.484	3.387
5	3	3.387	5.645	2.258
5	4	2.097	7.419	5.322
6	1	2.857	9.173	6.316
6	2	0.902	2.105	1.203
6	3	2.707	6.241	3.534
6	4	1.955	5.338	3.383

7	1	4.305	13.52	9.215
7	2	2.19	1.888	-0.302
7	3	1.586	3.097	1.511
7	4	2.19	6.269	4.079
8	1	1.987	15.103	13.116
8	2	2.305	7.711	5.406
8	3	0.556	2.385	1.829
8	4	3.418	8.108	4.69

Free Fatty Acids

Subject	SUB	Pre	Post	Delta
1	1	0.655	1.057	0.402
1	2	0.064	0.039	-0.025
1	3	0.405	0.075	-0.33
1	4	0.102	0.06	-0.042
2	1	0.491	0.866	0.375
2	2	0.141	0.054	-0.087
2	3	0.277	0.081	-0.196
2	4	0.184	0.205	0.021
3	1	0.346	0.703	0.357
3	2	0.085	0.115	0.03
3	3	0.053	0.056	0.003
3	4	0.075	0.077	0.002
4	1	0.875	0.801	-0.074
4	2	0.181	0.1	-0.081
4	3	0.239	0.176	-0.063
4	4	0.167	0.239	0.072
5	1	0.424	0.804	0.38
5	2	0.148	0.076	-0.072
5	3	0.476	0.098	-0.378
5	4	0.105	0.076	-0.029
6	1	0.202	0.365	0.163
6	2	0.108	0	-0.108
6	3	0.171	0.022	-0.149
6	4	0.108	0.156	0.048

7	1	0.441	0.704	0.263
7	2	0.119	0.082	-0.037
7	3	0.125	0.123	-0.002
7	4	0.093	0.106	0.013
8	1	0.216	0.773	0.557
8	2	0.151	0.094	-0.057
8	3	0.074	0.094	0.02
8	4	0.153	0.113	-0.04

Lactate

Subject	SUB	Pre	Post	Delta
1	1	1.5	0.744	-0.756
1	2	1.5	1.207	-0.293
1	3	1.56	0.362	-1.198
1	4	0.906	0.302	-0.604
2	1	0.835	0.533	-0.302
2	2	0.734	0.473	-0.261
2	3	0.745	0.654	-0.091
2	4	1.127	0.443	-0.684
3	1	0.469	1.134	0.665
3	2	0.461	0.64	0.179
3	3	0.622	0.786	0.164
3	4	0.469	0.622	0.153
4	1	1.004	0.535	-0.469
4	2	0.467	0.796	0.329
4	3	0.567	0.567	0
4	4	1.058	0.458	-0.6
5	1	0.599	0.498	-0.101
5	2	0.498	0.31	-0.188
5	3	0.579	0.399	-0.18
5	4	0.579	0.449	-0.13
6	1	0.959	1.188	0.229
6	2	1.309	0.739	-0.57
6	3	0.959	1.069	0.11
6	4	0.589	0.669	0.08

7	1	0.584	0.652	0.068
7	2	1.018	1.048	0.03
7	3	0.594	0.5035	-0.0905
7	4	0.584	0.342	-0.242
8	1	0.483	2.136	1.653
8	2	0.866	2.277	1.411
8	3	1.119	1.139	0.02
8	4	1.774	1.018	-0.756

Total Cholesterol

Subject	Time	Chol
1	1	209.2
1	2	198.4
2	1	221
2	2	151.6
3	1	200.2
3	2	201.6
4	1	200.5
4	2	174.7
5	1	204.2
5	2	182.7
6	1	155.2
6	2	158.5
7	1	217.3
7	2	198.7
8	1	154.5
8	2	129.9

HDL-Cholesterol

Subject	Time	HDL
1	1	51.3
1	2	62.4
2	1	66.1
2	2	66.1
3	1	69.1
3	2	86.4
4	1	47.8
4	2	55.1
5	1	58.8
5	2	58.8
6	1	49.6
6	2	62.1
7	1	59.2
7	2	65.4
8	1	47.9
8	2	48