

**BETA BLOCKADE AND THERMOREGULATION DURING EXERCISE IN
POST MENOPAUSAL WOMEN**

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Submitted to the University of Manitoba
in partial fulfillment of the degree requirements for the
Degree of Master of Science
in the Faculty of Physical Education

by

Shelley D. Sandiford
#6109449

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POST MENOPAUSAL WOMEN**

BY

SHELLEY D. SANDIFORD

**A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University
of Manitoba in partial fulfillment of the requirements of the degree
of
MASTER OF SCIENCE**

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CHAPTER ONE: INTRODUCTION

The elderly are the most rapidly growing segment of the population. Since women tend to live longer than men, a disproportionate number of adults living into old age are women (Fox, Bowers & Foss, 1989). Older individuals are encouraged to remain independent and to take advantage of the increasing number of community activities. Programs are available to help the elderly maintain or improve the ability to perform daily activities, to develop healthy lifestyles, and to maintain or improve their health and wellness as they continue ageing (Canadian Red Cross, 1996). Unfortunately, despite the growing quantity of programs, a large number of older individuals continue to remain inactive. Feelings of being too old and a lack of family support are common barriers to physical activity (Red Cross, 1996). An inactive lifestyle has many disadvantages, many of which are physical. The potentially harmful effects of a sedentary lifestyle intensify several physical characteristics associated with ageing. This includes a reduced thermoregulatory capacity, attributed to a diminished aerobic power (VO_2 max) and to the more direct effects of ageing on blood vessels and sweat glands.

When exercise and heat stress are considered together, research tends to suggest that the elderly show a decrease in sweat rate (Anderson & Kenney, 1987; Armstrong & Kenney, 1993; Inoue, Nakao, Araki, Murakami, 1991; Tankersley, Smolander, Kenny & Fortney, 1991) and skin blood flow (Armstrong & Kenney, 1993; Inoue, 1996; Kenney, 1988; Sagawa, Shiraki, Yousef & Miki, 1988; Tankersley et al., 1991), although these are not universal findings. These changes may lead to an increase in heat storage and a decrease in heat tolerance. Older women may be at an additional disadvantage due to the low levels of estrogen associated with post menopause. Past research indicates that estrogen may improve heat tolerance during exercise in the heat (Tankersley, Nicholas, Deaver, Mikita & Kenney, 1992) and that lower levels of this hormone may negatively alter the body's ability to thermoregulate (Baker, Dawson, Peters & Walker, 1994; Carpenter & Nunneley, 1988; Hessemer & Bruck, 1985; Lieberman, Gerhard, Uetata, Walsh, Selwyn, Ganz, Yeung & Creager, 1994;

1994; Tankersley et al., 1992).

Additional research has shown that older individuals who lead recreationally active lives fare better when subjected to exercise and heat stress than do older, untrained individuals (Buono, McKenzie & Kasch, 1991; Tankersley et al., 1991). Unfortunately, less attention has been paid to the application of the above findings to the lives of older individuals, and in particular, post menopausal women.

For example, prescription drug use, a common reality in the elderly (Johnson & Vollmer, 1991; Chrischilles, Foley, Wallace, Lemke, Selma, Hanlon, Glynn, Ostfeld & Guralnik, 1992), was overlooked in these studies, and the use of some medications may attenuate heat loss during exercise. In one study, 43.3% of the 65 to 94 year old subjects surveyed used cardiac agents and diuretics (Johnson & Vollmer, 1991). Another study reported that approximately 64% of older men and 73% of older women surveyed were using some form of medication (Chrischilles et al., 1992). Greater use of prescription drugs among older women than men is a universal finding (Chrischilles et al., 1992).

Beta blockers have been available for approximately 30 years, and are used for the treatment of angina pectoris, dysrhythmias, and most commonly, hypertension (Kostis & DeFelice, 1984). Ten to 15% of Canadians have controlled or uncontrolled high blood pressure, including 25% of persons 65 and over. Approximately 60% of physician/patient contacts for high blood pressure involve women (Health and Welfare Canada, 1986). Regular exercise has been suggested as a favourable lifestyle change for those with hypertension (Perez-Stable, Coates, Baron, Biro, Hauck, McHenry, Gardiner & Feigel, 1995; Seals, Silverman, Reiling, & Davy, 1997; Sleight, 1996) and can also improve thermoregulation during acute exercise in the heat (Gisolfi, Lamb & Nadel, 1993). Kushi, Fee, Falsom, Mink, Anderson & Sellers (1997) found that participation in moderate or vigorous activity one to four times per week was associated with decreased risk of death from respiratory and cardiovascular disease. Unfortunately, beta adrenoceptor blockade has been shown to have detrimental effects on subjects

exercising in the heat (Pescatello, Mack, Leach & Nadel, 1987; Pescatello, Mack, Leach & Nadel, 1990; Mack, Shannon & Nadel, 1986) as well as a negative effect on training programs (Ades, Gunther, Meacham, Handy & LeWinter, 1988; Sable, Brammell, Sheehan, Nies, Gerber & Horowitz, 1982). While other drugs are now available for the treatment of hypertension [as angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers] beta blockers are well proven and still remain the primary drugs in the treatment of patients with elevated blood pressure (Sleight, 1996). In light of the use of these drugs for the control of such problems, and the research suggesting that they may have a negative effect on thermoregulation, it is unfortunate that older women have been practically excluded from the research concerning exercise and heat stress. In this study, we examined the effects of beta blockade on thermoregulation in post-menopausal women during a cycle bout in the heat.

STATEMENT OF THE PROBLEM

The purpose of this study was to determine the effects of non-selective beta adrenergic blockade during moderate exercise in the heat on the aural canal temperature, skin temperature, skin blood flow and sweating responses of post menopausal women.

HYPOTHESES

1. Beta blockade would result in decreased average skin temperature, skin blood flow, sweat rate, heart rate and blood pressure compared to the placebo trial.
2. Beta blockade would result in significant heat storage (increased aural canal temperature) compared to the placebo trial.

DELIMITATIONS

This study was delimited to normotensive, post menopausal women who were apparently healthy and not undergoing hormonal replacement therapy.

LIMITATIONS

1. The method of subject selection was by recruitment rather than by random selection.
2. The data was collected on normotensive individuals which limited the generalizability of the results. Including hypertensive females, already using medication, would have been more applicable to real life, however, this was not realistic since medications and dosages would vary too much between subjects to be properly controlled.

ASSUMPTIONS

1. The dosage of the beta blocker administered was sufficient to determine the differences in thermoregulatory responses.
2. Aural canal temperature was a sensitive enough measure to determine the effects of beta blockade on heat storage.
3. The subjects adhered to the dosage recommendations, as well as other preparatory suggestions.

4. The screening procedures eliminated all high risk participants.

DEFINITION OF TERMS

Aural Canal Temperature (T_{AC})

Temperature measured near the tympanic membrane . It is an index of core temperature.

Average Skin Temperature (T_{SKavg})

A weighed average from various areas of the body. The following was derived from Layton et al. (1983):

$$T_{SKave} = 0.07 \text{ (forehead temperature)} + 0.0875 \text{ (upper back temperature)} + 0.0875 \text{ (lower back temperature)} + 0.0875 \text{ (chest temperature)} + 0.0875 \text{ (abdomen temperature)} + 0.095 \text{ (dorsal thigh temperature)} + 0.095 \text{ (anterior thigh temperature)} + 0.065 \text{ (calf temperature)} + 0.065 \text{ (anterior leg temperature)} + 0.07 \text{ (foot temperature)} + 0.05 \text{ (dorsal hand temperature)} + 0.14 \text{ (forearm temperature)}$$

B-adrenergic blocking drugs

Antagonists which appear to occupy the beta receptor while preventing continuing function by competitively inhibiting access of the agonist (Kostis & Defelice, 1984).

Blood Pressure

The main driving force for propelling blood to the tissues (Sherwood, 1989).

$$\text{MAP (mean arterial pressure)} = Q \times \text{TPR}$$

Where:

Q = Cardiac Output

TPR = Total Peripheral Resistance

Cholinergic

Nerve fibres that release acetylcholine. Both sympathetic and parasympathetic preganglionic

fibres release acetylcholine. Parasympathetic postganglionic fibres also release acetylcholine (Sherwood, 1989).

Core Temperature (T_{CORE})

Refers to the temperature within the heart, brain and central nervous system. It occasionally includes the temperature within the abdominal and visceral organs and is approximately 37°C.

Diastolic Blood Pressure (DBP)

The lowest pressure experienced in the arterial system during ventricular relaxation.

Forearm Blood Flow (FBF)

Measured by plethysmography, FBF is a combination of skin and muscle blood flow.

Hypertension

Individuals with blood pressure readings over 140/90mmHg (160/95mmHg for those over 60) (Sherwood, 1989).

Menopause

The permanent cessation of menstruation which is assumed to have occurred following a period of amenorrhea for 12 months (Khaw, 1992).

Normotensive

Those who have blood pressure readings between 100/60mmHg and 140/90mmHg (up to 160/90mmHg for those over 60) (Sherwood, 1989).

Skin Blood Flow (SKBF)

The amount of blood reaching the skin surface as measured by laser doppler flowometry (LDF).

Systolic Blood Pressure (SBP)

The maximum pressure in the arterial system which is experienced during ventricular contraction (Fox et al., 1989).

CHAPTER TWO: LITERATURE REVIEW

This review will examine some of the past research involving thermoregulation and ageing. Although the current research project included post-menopausal women only, the results of investigations using both male and female subjects are reviewed to obtain a clearer picture of the effects of ageing on thermoregulatory responses during exercise and heat stress. Literature in the area of beta adrenergic blockade and thermoregulation is also included in this review. Unfortunately, it is limited only to male participants as no studies involving post-menopausal women could be obtained. However, the studies used in this review supply insight regarding the effects of beta blockade on thermoregulatory responses.

TEMPERATURE REGULATION

Although normal body temperature is considered to be 37°C this tends to vary from person to person, and even within individuals, depending upon a variety of factors. Core tissues function best at 37 to 38°C (Sherwood, 1989). The skin and subcutaneous fat constitute the outer shell and their temperatures tend to be generally cooler than the core with a greater degree of acceptable variation. The temperature of the skin is deliberately varied as a measure to maintain core temperature (Sherwood, 1989). During exercise, the core temperature may rise as high as 40°C, and although this would be considered a fever in the resting person, it is normal during strenuous exercise.

Four mechanisms of heat transfer affect the body: radiation, conduction, convection, and evaporation. Radiation is the emission of heat energy from the surface of a warm body in the form of electromagnetic waves, which travel through space. Conduction is the transfer of heat between objects of differing temperatures which are in direct contact with each other. In this situation, heat moves down a thermal gradient from the warmer object to the cooler one. During this process the original warmer molecule loses some of its thermal energy as it slows down and cools off a bit. Therefore, given enough time, the temperature of the two touching objects eventually equalizes

(Sherwood, 1989). Convection refers to the transfer of heat energy by air (or water) currents. One of the most important methods of heat transfer for the adult exercising in the heat is evaporation. As water evaporates from the skin's surface, the heat required to transform water from a liquid to a gaseous state (the heat of vaporization) is absorbed from the skin thereby cooling the body. Although heat loss through non-sweating skin and the respiratory tract is considered insensible, sweating is an active evaporative heat loss process under sympathetic nervous control. The rate of evaporation can be adjusted by means of sweating as an important mechanism to eliminate excess heat as needed. Moreover, when environmental temperatures exceed skin temperature, sweating is the only avenue for heat loss, as the body will gain heat by radiation and conduction under these circumstances (Sherwood, 1989). The methods of heat transfer are summarized in Figure 2-1.

Pandolf, Sawka & Gonzales (1988) explain that the reflex control of heat dissipating responses (sweating, skin blood flow and forearm venous volume) depend on body core temperatures. The temperature controller is located within the hypothalamus, and these thermoregulatory responses depend on both core and mean skin temperatures. The sensitivity of these thermoregulatory responses to core temperature allows the thermoregulatory system to keep core temperature relatively constant (Pandolf et al., 1988) and allows the skin temperature of someone who enters a hot environment to rise and elicit sweating before any possible rise in core temperature. An increase in heat within the body (as during exercise) has relatively little effect on skin temperature and the appropriate heat dissipating method responds to an increase in core temperature. Once these thermoregulatory effector responses are sufficient to dissipate heat at the rate at which it is produced, thermal balance is restored so that core temperature stops increasing and reaches a steady state level. The rise in core temperature which elicits heat dissipating responses sufficient to re-establish thermal balance is called a load error (Pandolf et al., 1988). Both skin blood flow and sweating exhibit an internal temperature "threshold" beyond which they rise with increasing core and skin temperatures. Thermoregulation depends on an

integrated signal from central and peripheral structures. The first role of exercise in the control of skin blood flow is its thermogenic role, providing a stimulus for cutaneous vasodilation. This vasodilation promotes the transfer of heat from the core to the body surface, where sudomotor control of evaporative heat loss via sweating provides the final pathway for eliminating the metabolic heat production during dynamic exercise (Kenney & Johnson, 1992).

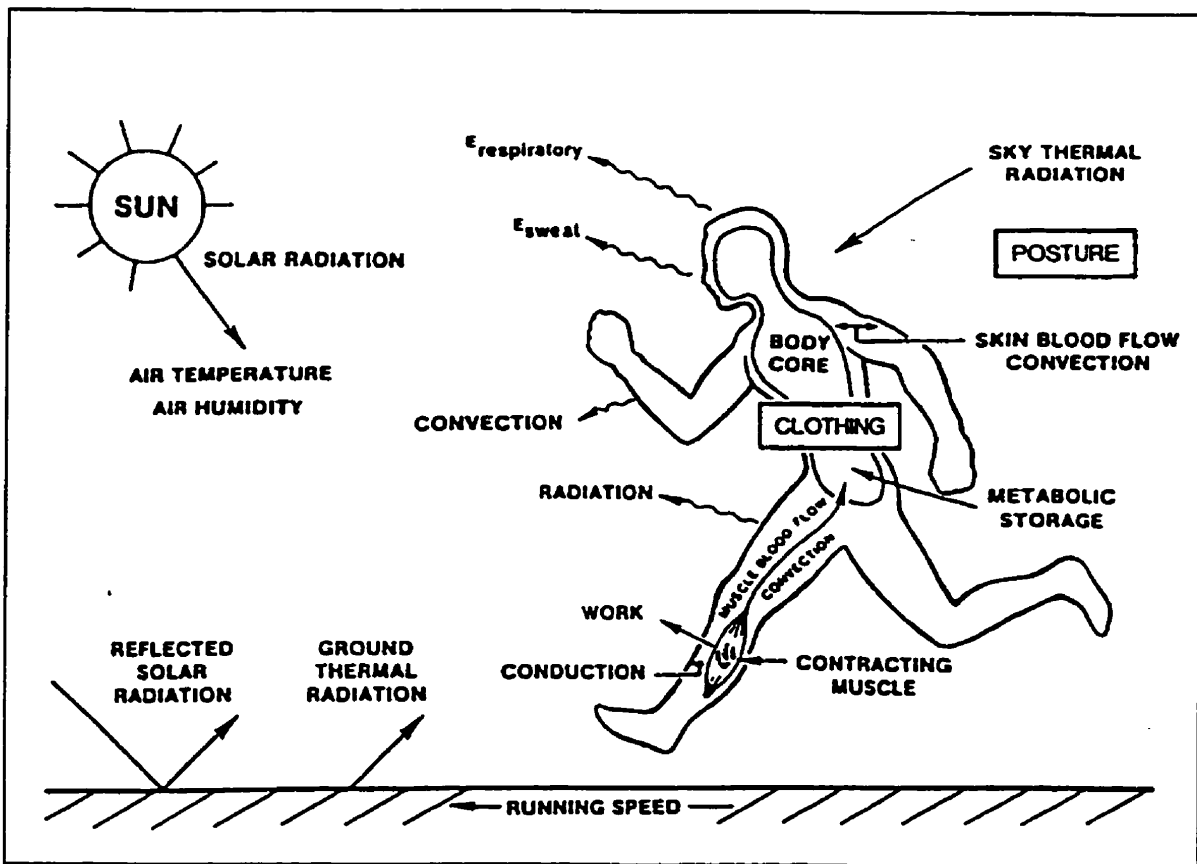


Figure 2-1: Summary of Heat Transfer Methods: From Pandolf et al. (1988)

During exercise, the rise in core temperature is proportional to the metabolic rate and nearly independent of environmental temperature over a fairly wide range. Core temperature increases during exercise as the consequence of a change in the regulatory adjustment of body temperature and not of an insufficient ability to dissipate heat. The body's thermostat is re-set at a higher level during exercise, and the core temperature thresholds for the thermoregulatory effector responses are elevated (Pandolf et al., 1988). When heat storage becomes sufficient to raise core temperature beyond the thresholds for vasodilation and sweating, heat transfer to the surface and elimination to the environment rapidly increases to match the metabolic heat production. At this stage, the rate of rise in core temperature is attenuated and approaches zero. For a given exercise intensity, achievement of thermal steady state is only possible within a certain range of environmental conditions, called the "prescriptive zone" (Kenney & Johnson, 1992).

The hypothalamus serves as the body's thermostat and is able to respond to temperature changes in the blood as small as 0.01°C . Changes of only a few tenths of 1°C in the temperature of the anterior preoptic area of the hypothalamus elicit changes in the thermoregulatory effector response, and this area contains many neurons which increase their firing rate in response to either warming or cooling (Pandolf et al., 1988). The hypothalamus is constantly updated of both skin and core temperature by means of specialized temperature-sensitive receptors called thermoreceptors. Peripheral warmth and cold receptors monitor skin temperature throughout the body and transmit information about changes in surface temperature to the hypothalamus. The core temperature is monitored by central thermoreceptors, which are located in the hypothalamus itself as well as elsewhere in the central nervous system and the internal organs and all of this information is integrated (Sherwood, 1989). Unless the heat stress exceeds the capacity of the thermoregulatory system, these responses will increase until they are sufficient to restore heat balance and prevent further increases in body temperature. The entire system is referred to as a negative feedback system (Pandolf et al.,

1988; Sherwood, 1989).

When humans are hot, the goal is to increase heat loss to the environment. The amount of heat lost to the environment by radiation and conduction-convection is determined largely by the temperature gradient between the skin and the external environment. The insulative capacity of the shell can be varied by controlling the amount of blood flowing through the skin. Blood flow to the skin serves two functions. First, it provides a nutritive blood supply to the skin. Secondly, as blood is pumped to the skin from the heart, it has been heated in the central core and carries this heat to the skin. In the process of thermoregulation, skin blood flow can vary tremendously, from 400 ml up to 2500 ml. The more blood reaching the skin from the warm core, the closer the skin's temperature is to the core temperature. Vasodilation of the skin vessels, which permits increased flow of heated blood through the skin, increases heat loss or, if the environmental temperature is above core temperature, facilitates heat gain. This skin vasomotor response is coordinated by the hypothalamus by means of sympathetic nervous-system output (Sherwood, 1989).

Heat exhaustion refers to a state of collapse (usually resulting in fainting), which is caused by reduced blood pressure brought about as a result of overtaxing the heat loss mechanisms. Extensive sweating reduces cardiac output by depleting the plasma volume, and pronounced skin vasodilation causes a drop in total peripheral resistance. Since blood pressure is determined by cardiac output and total peripheral resistance, blood pressure falls, an insufficient amount of blood is delivered to the brain, and fainting takes place. Therefore, heat exhaustion is a consequence of overactivity of the heat-loss mechanisms rather than a breakdown of the mechanisms. By forcing the body to stop activity when heat-loss mechanisms are no longer able to cope with heat gain through exercise or a hot environment, heat exhaustion serves as a safety valve to help prevent the more serious consequences of heat stroke (Sherwood, 1989).

In the heat, exercise becomes slightly more complicated because of the demands of the

cardiovascular system. The detrimental effects of heat exposure on performance of prolonged exercise are well recognized. Galloway & Maughn (1997) found that individuals cycling at 70% VO_2 max reached exhaustion significantly sooner at 31°C than at either 4°C, 11°C or 21°C. The mechanisms described for heat exhaustion above partially explain the results of that study. Blood supply must be available for both the working muscles and for thermoregulatory demands. Dynamic exercise creates a primary drive for redistribution of blood flow away from metabolically inactive tissues (including skin). However, since the energy expended by contracting muscle is also a source of heat, and since skin blood flow acts as a thermoregulatory heat dissipating response, there is a direct competition between the reflexes serving these two functions. Such competitive control is a natural characteristic of dynamic muscular exercise and is dependent upon the mode, intensity and duration of exercise (Kenney & Johnson, 1992). Since perfusion cannot be maintained, it is distributed to optimize thermal and exercise performance (Gisolfi et al., 1993). Although it has been suggested that aerobically trained individuals have more effective thermoregulatory responses to exercise and heat stress (Buono et al., 1991; Tankersley et al., 1991) a recent study by Yoshida, Nagashima, Nose, Kawabata, Nakai, Yorimoto & Morimoto (1997) found that heat distribution responses were more related to blood volume than aerobic power in college aged male track and field athletes.

Thermoregulatory Responses

While in the heat, the body prevents sharp rises in core temperature by redistributing the blood flow to the skin and through the initiation of sweating. Both increases in skin blood flow (convective cooling) and sweating (evaporative cooling) are effective heat loss mechanisms which allow an elevated core temperature to be sustained for some time (Gisolfi et al., 1993). The steady state core temperature and the cutaneous blood flow are dependent upon exercise intensity and the efficiency of sweating. At ambient temperatures below approximately 32°C to 34°C, increase in skin blood flow is the primary method of releasing body heat (convective). However, vasodilation for heat loss

is limited by the ambient conditions. When air temperatures are hotter than mean skin temperature, the gradient for heat exchange is reversed and heat is transferred from the air to the skin, resulting in heat storage rather than heat loss (Fortney & Vroman, 1985).

Non-Thermoregulatory Responses

At the onset of exercise, skin blood vessels vasoconstrict, as exercise shifts the threshold temperature for cutaneous vasodilation upwards. The shift in the relationship between increases in skin blood flow and core temperature may result from delayed onset of vasodilator activity, enhanced vasoconstriction, or a combination of both, although recent evidence suggests that the first possibility is more likely (Gisolfi et al., 1993). Kenney et al. (1991) determined that there was no difference in the onset of cutaneous vasodilation during exercise with α -adrenergic blockade, suggesting that adrenergically-mediated vasoconstriction did not play a role in the phenomenon. When subjects are heated passively at rest, the rise in skin blood flow appears to be linear, and without constrictions. However, under conditions of exercise, skin blood flow increases until the core temperature reaches approximately 38°C. At this point, cutaneous blood flow reaches a plateau, and the rise in skin blood flow is either attenuated or stopped (Gisolfi et al., 1993). Skin blood flow appears to be sacrificed to preserve or increase skeletal muscle blood flow at the initiation of exercise or during heavier exercise with heat stress. However, even muscle blood flow is constricted during severe conditions in which cardiac output is limited or unable to increase to match a demand, indicating that preservation of blood pressure appears to be a top priority over the preservation of either muscle or skin blood flow (Gisolfi et al., 1993).

MEASUREMENT OF BODY TEMPERATURES

The measurement of internal body temperature is extremely important in the study of thermoregulation and exercise. The temperature within a body depends upon the metabolic rate of the surrounding tissues, the source and magnitude of blood flow and the temperature gradients between various body regions (Pandolf et al., 1988). While there are several sites used by physiologists to measure core temperature, three of the most common appear to be esophageal temperature (T_{es}), rectal temperature (T_{re}), and tympanic temperature (T_{tym}).

Esophageal Temperature

Esophageal temperature is obtained by inserting a catheter containing a thermocouple or thermistor, through the nasal passage and into the throat and then swallowing it (Pandolf et al., 1988). The thermocouple is positioned at a distance of one-fourth the subject's height, a position that closely matches the level of the left atrium (Wenger, Roberts, Stolwijk & Nadel, 1975). At this level, not only are the heart and esophagus in contact and relatively isothermal (Pandolf et al., 1988), but placement at the point of locally maximum temperature renders T_{es} relatively insensitive to small displacements of the thermocouple (Wenger et al., 1975). Pandolf et al. (1988) note that since this method can be considered uncomfortable by some, a topical anaesthetic, is often used on the catheter and/or in the throat to alleviate some discomfort. Also mentioned is the need to use a fairly stiff plastic catheter that does not easily curl back on itself. The rapid response time of esophageal temperature is due to the low heat capacity of the esophagus and its proximity to the heart and is thus considered the best non-invasive measurement of core temperature for humans (Pandolf et al., 1988).

Rectal Temperature

Rectal temperature is often employed due to its increased comfort compared to Tes. It is obtained by inserting a temperature sensor a minimum of five centimetres past the anal sphincter. Placement is important since it has been established that depending upon the insertion depth, variability may be as high as 0.8°C (Pandolf et al., 1988). Another potential problem is that a poorly placed sensor may later slip to a depth less than five centimetres beyond the anal sphincter during muscular exercise. However this problem can be solved by attaching a bulb to the rectal catheter at the desired insertion depth, that will abut the anal sphincter internally (Pandolf et al., 1988). Rectal temperature values are often higher than values measured at other core temperature sites and is slow to respond to changes in blood and other core temperatures. Pandolf et al. (1988) state that the reason for this slow response may be due to a low rate of blood flow to the rectum compared to other measurement sites.

Tympanic Membrane Temperature

Tympanic membrane temperature is another option for core temperature measurement. A thermocouple is inserted into the ear canal where it is situated against the tympanic membrane. Although this method runs the risk of damaging the tympanic membrane during placement (Sato, Kane, Soos, Gisolfi, Kondo, & Sato, 1996), it has been suggested that tympanic temperature is an ideal core temperature site due to its proximity to the brain and the carotid artery. There have been strong arguments both for and against the use of tympanic temperature. Shiraki, Sagawa, Tajima, Yokota, Hashimoto & Brengelmann (1988) found that while tympanic temperature decreased during face cooling, brain temperature did not. Mariak, Lewko, Luczaj, Polocki & White (1994) found a direct relationship between measured human cerebral and tympanic temperatures during changes in brain temperatures. However, due to the increased comfort of this method over esophageal temperature, it is often chosen by researchers.

Aural Canal Temperature

Aural canal temperature (T_{AC}) is a variant of tympanic membrane temperature whereby the thermocouple is positioned close to the tympanic membrane instead of against it. .

Skin temperature

Skin temperature may be used for calculating the mean body temperature for heat storage determinations, calculating sensible (radiative and convective) heat exchange and skin conductance, or integrating into an index of the skin temperatures input to the thermoregulatory controller (Pandolf et al., 1988). Care needs to be taken to ensure that the temperature sensors are in good contact with the skin or the measurement may be biased by the ambient temperature (Pandolf et al., 1988). The average skin temperature (T_{skavg}) represents the sum of weighted individual skin temperatures. Layton, Mints, Annis, Rack, & Webb (1983) compared calorimetry using heat flux transducers with a suit calorimeter to derive a weighted 12-site formula to be used in the calculation of T_{skavg} . This study introduced the following formula:

$$T_{skavg} = 0.07 \text{ (forehead temperature)} + 0.0875 \text{ (upper back temperature)} + 0.0875 \text{ (lower back temperature)} + 0.0875 \text{ (chest temperature)} + 0.0875 \text{ (abdomen temperature)} + 0.095 \text{ (dorsal thigh temperature)} + 0.095 \text{ (anterior thigh temperature)} + 0.065 \text{ (calf temperature)} + 0.065 \text{ (anterior leg temperature)} + 0.07 \text{ (foot temperature)} + 0.05 \text{ (dorsal hand temperature)} + 0.14 \text{ (forearm temperature)}$$

HUMAN SWEAT GLAND FUNCTION AND EVAPORATIVE HEAT LOSS

When ambient temperature increases, there is a greater dependence upon insensible (evaporative) heat loss to protect core temperature during exercise. The eccrine glands secrete sweat onto the skin surface which causes evaporative cooling when it is converted from liquid to water vapour. Thermoregulatory sweat in humans is secreted by four million eccrine glands and the number of sweat glands per unit of skin surface area varies considerably between body regions (Pandolf et al., 1988). The structure consists of the secretory coil, duct, and skin pore. The amount of sweat secreted by the gland depends upon the structure and function of the stimulated gland, as well as the sudomotor signal from the central nervous system. It has been determined that individuals who consider themselves heavy sweaters have larger eccrine glands, and indeed the size of the sweat gland can vary as much as fivefold among different individuals. As well, as the sweat gland size increases there is greater maximal sweat per gland, greater sweat rate per unit tubular length or unit volume of the secretory coil, and a greater cholinergic sensitivity of the sweat gland (Pandolf et al., 1988). Maximal sweat rate ranges from 2 to 20 nL/min for each gland (Gisolfi et al., 1993).

Neural Control of the Sweat Gland

The sudomotor signal descends through the brain stem and spinal tracts to exit into the paravertebral fibres ganglionic chain. The post-ganglionic sympathetic fibres which innervate the eccrine gland are non-myelinated class C fibres that are primarily cholinergic (Pandolf et al., 1988; Gisolfi et al., 1993). These glands respond primarily to thermal stress through sympathetic cholinergic stimulation. However, it appears that circulating catecholamines (especially epinephrine) facilitate thermoregulatory sweating as there are alpha and beta adrenergic receptors associated with eccrine sweat glands (Pandolf et al., 1988). It is also known that ATP coexists with norepinephrine and acetylcholine and may function as a co-neurotransmitter. Vasoactive intestinal peptide (VIP), atrial natriuretic peptide (ANP), calcitonin gene-related peptide (CGRP), and galanin have also been localized

in the periglandular nerves (Gisolfi et al., 1993). Thermoregulatory sweating can begin within a few seconds to minutes of starting muscular exercise. As the sweat rate increases to maximum levels, first there is a recruitment of sweat glands and then an increase in the sweat secretion per gland. Individual regions of skin have different sweating responses for a given core temperature. For a given core temperature, the back and the chest have the greatest sweating rates. Conversely, the limbs will have relatively high sweat rates only after substantial elevation in core temperature (Pandolf et al., 1988).

The physiological mechanism by which elevated local skin temperature enhances sweating is unclear. One possibility is local skin heating results in a greater release of neurotransmitters for a given sudomotor signal arriving at the eccrine sweat gland. The increased neurotransmitter release would stimulate greater sweat production and release. Gisolfi et al. (1993) noted that it has also been shown that local heating increases the responsiveness to a given amount of neurotransmitter. It is unknown if this increased responsiveness is receptor mediated or reflects increased cellular metabolism within the secretory coil (Pandolf et al., 1988). According to Gisolfi et al. (1993) other possibilities for the effects of local skin heating on the sweat gland may include glandular metabolism, or the affinity of receptors to agonists, and/or membrane transport. It should be noted that the rate of sweat evaporation depends upon air movement and water vapour pressure gradient between the skin and the environment, so that sweat tends to collect on the skin in still or moist air. Wetting the skin surface causes a decrease in sweat secretion, an effect called hidromeiosis (Pandolf et al., 1988). This phenomenon, defined as the decline of sweat rate during repeated or prolonged sweating has long been known to occur, but it still is not known whether hidromeiosis is decreased sweating due to poral occlusion, sweat gland fatigue, or more specific mechanisms (Gisolfi et al., 1993).

Variables Influencing Sweat Gland Function

Physical training improves glandular function. Sweat rates are commonly higher in trained men and women than in their untrained counterparts. Peripheral sweat rate has also been significantly correlated with maximal oxygen uptake. Heat acclimatized individuals are capable of preventing a critical decrease in blood volume during exercise by retaining protein to expand the initial plasma volume. A high initial plasma volume ensures an adequate cardiac filling pressure (even with increased filtration of plasma water out of the vascular compartment and the eventual loss of water as sweat). Since hypovolemia negatively effects sweat gland function, both improved glandular activity and cardiovascular responses complement each other to enhance thermoregulatory capacity after acclimatization or physical exercise (Gisolfi et al., 1993).

Buono & Sjoholm (1988) studied the effect of physical training on peripheral sweat production. Forty subjects were divided into four subgroups: Ten sedentary men (26 ± 4 years), ten sedentary women (22 ± 3 years), ten endurance trained men (26 ± 3 years), and ten endurance trained women (25 ± 3 years). The trained groups had significantly higher VO_2 max values than the untrained subjects. No difference in sweat production was found between either the sedentary men and the sedentary women, or the trained men and the trained women. However, the trained individuals produced significantly more sweat per gland than their sedentary counterparts. The major finding of this study was that physical training appeared to improve the secretory activity of the human sweat gland. This was based on the fact that when no obvious central thermoregulatory drive was involved the peripheral sweat production of trained individuals was greater than that of sedentary subjects. Furthermore, sweat rate was significantly correlated with VO_2 max.

Ageing and Sweat Gland Function

Ageing appears to have very little effect on the pharmacologically induced maximal sweat rate until the sixties, but glandular function gradually declines in the seventies and eighties. Even though it has been shown that the elderly may have trouble maintaining core temperature while exercising in the heat, as demonstrated in the examples below, this problem appears to be markedly reduced with exercise training and the maintenance of a relatively high maximal oxygen uptake (Gisolfi et al., 1993; Inoue, 1996).

There appear to be changes within the human sweat gland, and its function, with ageing as several studies suggest that the elderly may have a less effective sweating response in the heat. Decrease in sweating efficiency is evidenced by reductions in sweat rate and greater core temperatures at the onset of sweating. Indeed, it has been shown that older individuals have a larger null-zone (a range of core temperatures across which sweating and shivering effector responses are absent) than their younger counterparts (Anderson, Meneilly & Mekjavic, 1996). Many studies show decreases in sweat rate among older subjects (Buono et al., 1991; Tankersley et al., 1991; Armstrong & Kenney, 1993; Anderson & Kenney, 1987), but these findings are not universal (Drinkwater, Bedi, Loucks, Roche, & Horvath, 1982; Kenney, 1988; Inoue et al., 1991; Sagawa et al., 1988). It should be noted that those studies in which no differences in sweat rate were found tended to involve passive heating methods (Sagawa et al., 1988; Drinkwater et al., 1982; Inoue et al., 1991) and or protocols using humid conditions where sweating may be less effective for all subjects (Drinkwater et al., 1982; Kenney, 1988). Studies demonstrating more of a discrepancy between younger and older subjects tended to include protocols where heat stress and exercise were combined (Tankersley et al., 1991; Armstrong & Kenney, 1993; Anderson & Kenney, 1987).

Training and acclimation appear to slow the effects of ageing on the sweat gland (Armstrong & Kenney, 1993). In a comparison of older highly fit, older normally fit, and younger normally fit men,

Tankersley et al. (1991) found the sweat rate of the highly fit older men was intermediate to that of the other two subject groups. However, it remained unclear whether the decreased sweat rate/Tes slope of the normally fit older subjects was due to their lower VO_2 max or to some other ageing process. Buono et al. (1991) also determined that trained men tended to show less of a decrease in sweat rate with ageing. Inoue (1996) followed physically active elderly women in their sixth and seventh decades of life to determine the effects of increasing age on regional sweating responses. The longitudinal nature of this study made it unique. It was found that in response to passive heat stress, sweat gland function decreased despite maintaining physical characteristics and aerobic fitness. There was a decrease in total body sweat rate, sweat gland output and sweating sensitivity in various areas of the body. Results suggested that decrements may not occur uniformly over the body and may well spread from the lower limbs to the trunk. Therefore caution must be taken when interpreting the results of temperature regulation and ageing studies.

While cardiovascular conditioning plays a role in the sweating response, it appears that other factors may be operating within the ageing sweat gland. The decline in sweat rate has been partially attributed to a decrease in the number of active sweat glands with age (Kenney & Hodgson, 1987) or a diminished flow per heat activated sweat gland rather than any significant decrease in sweat gland number or density (Anderson & Kenney, 1987; Inoue, 1996). The latter theory holds more promise. Kenney & Fowler (1988) examined the age related differences in methylcholine (MCh) activated sweat gland density and output across three groups of heat acclimated men matched for VO_2 max and body composition. Methylcholine, an analogue of acetylcholine, was expected to bind to cholinergic receptor sites on the gland, leading to sweat secretion. It was hypothesized that sweat gland output, but not density would be lower in the older men. The subjects walked or ran on a treadmill or cycle ergometer at an intensity of 40 to 60% VO_2 max. It was determined that MCh caused a lower sweat output per gland in older men and that this decrement was unrelated to VO_2 max, altered

body composition associated with ageing, nor was it an artifact of a lower acclimation state. It was concluded that a decreased cholinergic sweating response is a function of ageing per se and the site of the alteration is at the level of the eccrine gland.

Measurement of Sweating Rate

The two main methods profiled here will include 1) the employment of a device which uses the hygroscopic properties of certain materials and their resistance change and moisture, and 2) the use of an automatic dew point sensor to measure sweating rate.

Bullard (1962) proposed a method whereby air of absolute (0%) humidity was passed over selected skin areas at a fixed flow rate. The change in water content of the air was then dependent upon the sweating rate, provided that air flow was adequate and relative humidity (RH) was low enough to maintain complete and rapid evaporation. The amount of water evaporated was calculated from the relative humidity change (RH) in the air as it passed over the skin, the air flow rate, and the temperature:

$$\text{sweating rate (mg/min)} = \text{air flow (litre/min)} \times (\text{RH} \div 100) \\ \times \text{density of sat. stream (in mg/liter)}$$

The relative humidity was determined with narrow range humidity-sensing elements. The elements contained a thin hygroscopic film of lithium chloride which decreased resistance with an increase in water vapour tension.

Graichen, Rascati & Gonzales (1982) described the use of a dew-point sensor consisting of a commercially available Peltier module, having an electrically conductive top. As the module was cooled to the dew point, water vapour would accumulate on the surface, lowering the resistance between the conducting plates. This change in surface resistance was detected by a high-impedance amplifier circuit, which in turn activated a servo amplifier and appropriate circuitry to reverse the

current flow through the Peltier module. Deposited water vapour would then be evaporated and resistance would drop, starting the cooling cycle again. The surface of the module would stabilize at the dew-point temperature, and this temperature would be measured. The sweating rate was then calculated using the ideal gas law:

$$\text{sweating rate} = (\text{change in } P_{\text{H}_2\text{O}})(AF)/(R_w \cdot A \cdot T) \text{ g} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$$

Where:

Change $P_{\text{H}_2\text{O}}$ = water vapour pressure gradient between inlet air and the water vapour pressure seen by the dew-point sensor

R_w = gas constant for water vapour 3.464 (Torr·l·g⁻¹·K⁻¹)

A = area of a sweat capsule enclosing a skin site (cm²)

T = absolute temperature (K) of dew point

AF = air flowing through the capsule (l·min⁻¹)

SKIN BLOOD FLOW

Skin blood flow carries heat by convection between the deep body tissues and the skin. In situations where core and skin temperatures are low enough that sweating does not occur, increasing skin blood flow brings skin temperature nearer to blood temperature, and decreasing skin blood flow brings skin temperature nearer to ambient temperature (Pandolf et al., 1988). In this situation, the body is able to control sensible (convective and radiative) heat loss by varying skin blood flow and therefore skin temperature. In conditions where sweating does occur, skin blood flow continues to increase with core or skin temperature. However, in these conditions, the tendency of skin blood flow to warm the skin is balanced by the tendency of sweating to cool the skin. Therefore, there is usually very little change in skin temperature and sensible heat exchange after sweating has begun, and skin blood flow serves to deliver to the skin the heat that is being removed by sweat evaporation (Pandolf et al., 1988). Skin circulation is affected by temperature in two ways:

- 1) Local skin temperature affects the vascular smooth muscle directly.
- 2) Temperatures in the core, and skin temperature elsewhere on the body, affect skin blood flow by reflexes operating through the sympathetic nervous system.

Blood flow in much of the human body is under dual vasomotor control. During heat exposure, vasodilation depends upon intact sympathetic innervation. This is referred to as active vasodilation as it depends upon the action of neural signals (Pandolf et al., 1988). The vasoactive agonist responsible for active cutaneous vasodilation in man has not yet been identified although it is believed that active vasodilation involves a cholinergic mechanism (Fortney & Vroman, 1985). However, a more recent study supplies evidence of beta adrenoceptors in the cutaneous vasculature (Crandall, Etzel, & Johnson, 1997). Skin vasodilation has been linked to the sweat gland release of bradykinin, and vasoactive intestinal peptide (VIP) although there are valid arguments for and against such mechanisms (Pandolf et al., 1988). Johnson et al. (1986) noted that onset times of sweating and

active vasodilation are nearly simultaneous and that active vasodilation is absent in areas of skin either congenitally or pathologically lacking sweat glands (Johnson, Brengelmann, Hales, Vanhoutte & Wenger, 1986; Fortney & Vroman, 1985). However, Fortney & Vroman (1985) stated that other investigators have found that vasodilatory response does not always depend upon local activation of sweat glands and bradykinin therefore cannot be the sole mediator in the vasodilatory response. The active vasodilation in skin appears to be primarily a sympathetic response, with modifying influences exerted by factors associated with rising body temperature and activation of sweat glands (Fortney & Vroman, 1985; Patterson, Warlter, & Taylor, 1994). Acetylcholine has also been shown to stimulate sweating, which may be linked with cutaneous vasodilation (Gisolfi et al., 1993). There are some cutaneous vascular beds (like that of the rabbit) which require endogenous nitric oxide for vasomotor nerve-induced vasodilation and that bradykinin appears to act through a nitric oxide mechanism. However, the mechanism by which nitric oxide formation might be enhanced during thermal stress remains unknown (Gisolfi et al., 1993). Skin vasoconstriction is activated through adrenergic sympathetic neurons (Johnson et al., 1986).

Local temperature acts on the skin blood vessels in at least two ways. First, local cooling potentiates, and heating weakens, the contractile response of vascular smooth muscle to norepinephrine and other adrenergic contractile agonists, apparently by changing the affinity of α -2 adrenergic receptors for these agonists. Second, in the human forearm, skin local heating causes vasodilation, and local cooling causes vasoconstriction, even in the absence of nervous signals (Pandolf et al., 1988; Johnson et al., 1986). The combined action of locally and reflex-mediated vasodilation results in levels of forearm blood flow subject to the limit that can be reached through the influence of each independently. Therefore, a locally heated forearm will show further increases in forearm blood flow if the subject becomes hyperthermic, but not if forearm blood flow has already reached maximum levels (Johnson et al., 1986).

Older Individuals and Skin Blood Flow

Ageing affects skin blood flow as well as sweat gland function. While varying results can be found in those studies comparing the sweating response of older and younger subjects, the findings concerning skin blood flow tend to be slightly less controversial. In those studies summarized for this review, all found decreases in skin blood flow during exercise and or heat stress (Sagawa et al., 1988; Tankersley et al., 1991; Armstrong & Kenney, 1993; Kenney, 1988; Kenney & Ho, 1995). This is demonstrated by an attenuation of the FBF-Tes relationship in older subjects. Kenney & Ho (1995) found that age alters the control of splanchnic blood flow at moderate (60% VO_2 peak) exercise intensities, such that less vasoconstriction occurs in older subjects. During 50 minutes of cycle exercise, it was found that significantly less net blood flow was redistributed away from splanchnic and renal vascular beds than in the younger subjects.

Training also appears to have an effect on skin blood flow. Tankersley et al. (1991) found the forearm blood flow measurements of highly fit older men to be intermediate to those measurements of normally fit older and normally fit younger individuals. Many researchers have hypothesized that there must be direct changes in the blood vessel itself with ageing, but the precise mechanism is not understood.

Kenney & Havenith (1993) explained that matching younger and older subjects with respect to as many physical and physiological characteristics as possible is important in studying whether ageing per se alters skin blood flow. Older individuals increase forearm blood flow to a significantly smaller degree than do younger subjects. One theory for the smaller increase in forearm blood flow was that increased sympathetic vasoconstrictor tone may limit heat-induced skin vasodilation in older individuals. Since vasoconstrictor tone in humans is mediated through alpha adrenergic sympathetic pathways, it was hypothesized that blocking vasoconstriction would normalize forearm blood flow of the elderly to that of younger subjects. However, blocking alpha receptors with a selective α_1 -

antagonist resulted in no selective effect on the skin blood flow response of older men (Kenney et al., 1991). It should be noted however, that the smaller increase in skin blood flow does not necessarily translate into greater heat storage or poorer heat tolerance (Kenney & Havenith, 1991; Kenney & Ho, 1995).

Blood Flow During Exercise and Heat Stress

During exercise in the heat, the higher skin blood flow will generally result in higher cardiac output. In healthy individuals, the cardiovascular strain associated with heat stress results mostly from decreased cardiac filling and stroke volume, which require a higher heart rate to maintain cardiac output (referred to as cardiovascular drift). The venous bed of the skin is large and compliant and dilates reflexly during heat stress. These vessels become engorged with blood and large volumes of blood pool in the skin, therefore displacing blood from the thorax, decreasing central blood volume, and cardiac filling (Pandolf et al., 1988). Since about 70% of the blood volume in an upright human is below heart level, it is in the upright position that the cardiovascular effects of blood pooling are greatest (Pandolf et al., 1988).

Exercise and heat stress affect the plasma volume by causing fluid movement between plasma and tissues. These fluid movements can occur quickly (well before any substantial losses of fluid have occurred by sweating). The overall magnitude and direction of these fluid movements depend on a number of factors, such as temperature, exercise type and intensity, hydration level, and status of heat acclimation. Also, much fluid is lost by sweating during exercise and heat stress. Since the main solute in sweat is sodium chloride, a disproportionately large fraction of water in sweat will be lost at the expense of extracellular fluid, including plasma, to the extent that the body's sodium content is reduced. If the water and salt lost by sweating are not replaced, plasma and extracellular fluid volumes will be progressively decreased during exercise heat stress (Pandolf et al., 1988).

There are many reflex adjustments that compensate for peripheral pooling of blood and

possible decreases in plasma volume, and help to maintain cardiac filling, cardiac output and arterial pressure during exercise in the heat. Splanchnic and renal blood flows are decreased substantially during exercise and this reduction is proportional to the relative exercise intensity (% VO_2 max). This allows for a corresponding diversion of cardiac output to the skin and the exercising muscle (Pandolf et al., 1988). During very high cardiovascular strain skin blood flow at a given core and skin temperature is known to be decreased during exercise. However, at moderate skin temperatures, the relation of forearm blood flow to core and skin temperatures is independent of exercise intensity over a range from mild to fairly intense exercise (Patterson et al., 1994). Skin blood flow appears to be compromised only at fairly high exercise intensities (Pandolf et al., 1988; Gisolfi et al., 1993). At a given level of skin blood flow, the volume of blood that pools in the cutaneous vessels depends on the compliance of the cutaneous veins, and therefore, can be decreased by constriction of these veins. With light to moderate exercise, the cutaneous veins constrict at the beginning of exercise, but relax within a few minutes (possibly in response to the increase in core temperature). However, cutaneous venous volume appears to be more sensitive to exercise than skin blood flow and the venoconstriction during more intense exercise is sustained. All of these adjustments discussed above help to maintain cardiac filling and cardiac output during exercise in the heat. Also sympathetic stimulation of the heart increases the rate and force of contraction, and therefore contributes further to maintaining cardiac output under these conditions (Pandolf et al., 1988).

Exercise acts as a non thermoregulatory factor to influence cutaneous blood flow in three ways (Gisolfi et al., 1993):

- 1) Blood vessels in the skin vasoconstrict at the onset of exercise. This occurs to redistribute blood flow to the working muscles. Since the skin vasodilator system is virtually inactive at rest in humans it is generally assumed that skin blood vessel vasoconstriction results from the activity of the skin vasoconstrictor system. This vasoconstriction is much more noticeable if exercise begins after skin

blood flow has already been elevated by whole body heat stress, at least to a point. Above local temperatures of 39°C there is a decrease in the response such that at 42°C or 44°C, there is little or no vasoconstriction at the onset of exercise (Johnson et al., 1986).

2) Exercise shifts the threshold temperature for cutaneous vasodilation upwards.

The shift in the relationship between skin blood flow and core temperature may result from a delay in vasodilation, enhanced vasoconstriction, or both. Recent evidence suggests that delayed vasodilation may be the more realistic possibility (Gisolfi et al., 1993).

3) Cutaneous blood flow fails to increase at very high core temperatures. Since skin blood vessel vasodilation and the resultant loss of heat occurring late in exercise is prohibited when cardiac output is restricted it appears that the maintenance of blood pressure in the face of increased blood flow to exercising limbs takes priority over skin vasodilation and heat loss (Gisolfi et al., 1993; Patterson et al., 1994). This plateau in skin blood flow (as with the delay in vasodilation at the onset of exercise) probably results from changes in active vasodilator activity, not vasoconstrictor activity. This is believed to be the case due to research determining that systemic α -1 adrenergic blockage does not alter blood flow during prolonged exercise with thermal stress (Gisolfi et al., 1993). Therefore, at high levels of exercise during heat stress, sweating dominates the body's heat transfer response (Johnson et al., 1986).

Measurement of Blood Flow

In 1953, Whitney gave rise to a new method of estimating blood flow through recording limb volume changes indirectly by the measurement of corresponding changes in limb dimensions. Whitney (1953) reasoned that if the transverse section of a human limb was truly circular and the shape of the section remained unaltered during expansion or contraction, then the percentage change in the area of the section would be twice the percentage change of the circumference of the section for small changes in area. However, this theory involved two important assumptions:

- 1) The length of the limb would remain unaltered during volume changes (which seemed indisputable)
- 2) the transverse sectional shape would remain unaltered during volume changes. This assumption presented more of a problem for Whitney (1953) due to the irregular shapes of human limbs. There was also no data determining the changes of shape, if any, which occurred in human limbs during volume changes.

The original apparatus consisted of a mercury-in-rubber resistance strain gauge. The voltage output of the strain gauge bridge for a given percentage change in length of the gauge was dependent on the voltage applied to the bridge circuit and on the type of galvanometer used for recording the output. Changes in limb volume were recorded by deflections of the galvanometer about the null position, which corresponded to the initial limb girth and volume. Usually a continuous record would be required and a photographic recording from a mirror galvanometer was used for this purpose. The gauge, if properly calibrated, was capable of measuring circumference changes in elastically deformable objects of cylindrical or subcylindrical shape.

Wenger, Roberts, Stolwijk & Nadel (1975) measured forearm blood flow during cycle exercise by venous occlusion plethysmography, using electrocapacitance plethysmography to register volume changes in the forearm. This was done by attaching a capacitance cuff to the forearm. A pneumatic collecting cuff was applied to just proximal to the capacitance cuff. The collecting cuff was inflated periodically to a pressure of 50-70 Torr with air from a reservoir at suitable pressure. Each inflation lasted 5-8 seconds. Since sweating beneath the cuff would alter the plethysmographic calibration, a thin sheet of polyethylene was applied between the capacitance cuff and the forearm. For measurement purposes, the arms were pronated, with the wrist partly dorsiflexed and the fingers comfortably flexed about a conforming lump of a sealing compound with the consistency of modelling clay. Such support of the fingers and wrist greatly reduced contraction of the forearm muscles as a

source of artifacts in the plethysmographic record. The arm was supported at the shoulder level, and the position of the chair was such that the subject did not have to brace the trunk while pedalling. Therefore, the plethysmographic records were almost always free of pedalling artifacts (Wenger et al., 1975). Many of the studies reviewed in the rest of this paper employed cycle exercise as opposed to treadmill walking in order to restrict movement of the forearm during exercise.

A more recent method of measuring skin blood flow is referred to as laser doppler flowometry (LDF). This method depends on the doppler shift of laser light reflected from the tissue. The frequency shift is due to the velocity of moving particles (red blood cells) within the tissue and is therefore, related to blood flow. This method relies on the average frequency shift normalized with respect to the unshifted signal from stationary tissue. It is specific to tissues less than 1.5mm in depth. Thus, there should be no contribution from blood flow in deeper tissues to the laser-derived flow signal (Johnson, Taylor, Shepherd & Park, 1984; Saumet, Kellogg, Taylor & Johnson, 1988). Since LDF is the newer method, comparisons have been made with the more conventional plethysmography. Johnson et al. (1984) found that although the relationship between plethysmographic and LDF recordings were quite linear, a given level of LDF could not be associated with a unique value of forearm blood flow (FBF). Therefore it was concluded that LDF measurements appeared to be more qualitative than quantitative. The advantages of LDF over plethysmography include the fact that continuous measurements can be made, measurements are not confined to the limbs and LDF measures skin blood flow to a specific area as opposed to FBF (which includes both skin and muscle blood flow). However, an advantage of plethysmography is that blood flow is expressed in traditional units (ml/100ml x min) rather than in terms of volts (V).

BARORECEPTORS

Before discussing the effects of beta blockade on heat tolerance and exercise performance it is important to address the relevance of baroreceptors in exercise. Baroreceptors closely monitor mean arterial pressure within the circulatory system. When deviations from normal are detected, multiple reflex responses are initiated to return the arterial pressure to normal. Short term (within seconds) adjustments are accomplished by alterations in cardiac output and total peripheral resistance mediated by means of autonomic nervous system influences on the heart, veins, and arterioles. Long term (requiring minutes to days) control involves adjustments in total blood volume, the magnitude of which has a profound effect on cardiac output (Sherwood, 1989). Like any reflex, the baroreceptor reflex includes a receptor, an afferent pathway, an integrating centre, an efferent pathway and effector organs (Sherwood, 1989).

The most important receptors involved in moment-to-moment regulation of blood pressure are located in the carotid sinus and in the aortic arch. Baroreceptors are mechanoreceptors sensitive to changes in both mean arterial pressure and pulse pressure. The integrating centre that receives the afferent impulses about the status of arterial pressure is the cardiovascular control centre located in the medulla within the brain stem. The cardiovascular control centre alters the ratio between sympathetic and parasympathetic activity to effector organs which include the heart and blood vessels (Sherwood, 1989).

Blood Pressure

Mean arterial blood pressure (MAP) is the main driving force for propelling blood to the tissues. Pressure must be closely regulated for two reasons:

- 1) It must be high enough to assume sufficient driving pressure, without which the brain and heart do not receive adequate flow.
- 2) The pressure must not be so high that it creates extra work for the heart and increases the

risk of vascular damage and possible rupture of small blood vessels.

Regulation of MAP is accomplished by controlling cardiac output (Q), total peripheral resistance (TPR) and blood volume:

$$\text{MAP} = \text{Q} \times \text{TPR}$$

If TPR decreases and MAP (blood pressure) is to remain constant, then Q must increase (Sherwood, 1989). Blood flow to any given tissue depends on the degree of vasoconstriction of the tissue's arterioles, and on the driving force of the MAP. Since MAP depends on Q and the degree of arteriolar vasoconstriction, if the arterioles in one tissue dilate, the arterioles in another tissue will have to constrict to maintain adequate arterial blood pressure to provide a driving force to push blood not only to the vasodilated tissue, but also to the heart and brain (Sherwood, 1989). If blood pressure is too low, the baroreceptors firing rate slows down and it increases if blood pressure is too high. The baroreceptors constantly provide information about blood pressure. They continuously generate action potentials in response to ongoing pressure within the arteries.

Upon being signalled by increased afferent firing that arterial pressure has become too high, the cardiovascular control centre responds by increasing parasympathetic activity and decreasing sympathetic activity to the cardiovascular system. These efferent signals decrease heart rate and stroke volume, and produce arteriolar and venous vasodilation, which in turn lead to a decrease in Q and a decrease in TPR (with a subsequent decrease in blood pressure back toward normal). When blood pressure decreases, baroreceptor activity decreases, and the cardiovascular control centre responds by decreasing parasympathetic activity while increasing sympathetic activity. The result is an increase in heart rate and stroke volume along with arteriolar and venous vasoconstriction. Therefore there are increases in both Q and TPR, and an increase in blood pressure back to normal (Sherwood, 1989).

Gisolfi et al. (1993) addressed the question of why baroreceptors do not act to limit exercise induced increases in blood pressure by offering the following theories:

- 1) Baroreflexes are required to initiate the cardiovascular responses to exercise.
- 2) Baroreflexes "turn off" with the initiation of exercise allowing heart rate and blood pressure to reach new, higher levels.
- 3) Baroreflexes reset to defend a new, elevated arterial pressure (Gistolfi et al., 1993).

BETA BLOCKADE

Two beta (β) adrenoceptor subtypes are noted by Gordon & Duncan (1991), β -1 and β -2. The main subtype found in the heart is β -1, while β -2 adrenoceptors predominate in the peripheral vasculature and in the lungs, where they mediate vasodilation and bronchodilation respectively. The development of β -1 selective blockers are regarded as important for those with asthma or peripheral vascular disease because β -2 adrenoceptors would remain relatively unblocked and responsive to sympathetic stimulation (Gordon & Duncan, 1991). Pritchard & Tomlinson (1986) noted that cardioselectivity may be have been more relevant in some vascular beds, where β -2 receptors were more important (as in muscle) than in others where β -2 receptors were not thought to be present (as in the skin). More recent research however has suggested that β -2 receptors may indeed be housed in the skin (Crandall et al., 1997).

Beta blockers are used to treat several cardiovascular disorders, including effort-induced angina, heart rhythm disturbance and high blood pressure. By blocking certain actions of the sympathetic nervous system, these drugs:

- 1) Reduce rate and contraction force of the heart, lowering ejection pressure of the blood leaving the heart and reducing the oxygen requirement for heart function.
- 2) Reduce the degree of contraction of blood vessel walls, resulting in the their expansion and consequent lowering of blood pressure.
- 3) Prolong the conduction time of nerve impulses through the heart, of benefit in the

management of certain heart rhythm disorders (Long & Rybacki, 1995).

There is a reduction in resting peripheral blood flow (as a measure of forearm blood flow) and an increase in peripheral resistance from non-selective beta blockade. This effect is believed to be due to a reduction in resting cardiac output (via a reduced heart rate). However, the fall in peripheral blood flow does not appear to be uniform throughout all vascular beds (Pritchard & Tomlinson, 1986). Pritchard & Tomlinson (1986) claim there is also evidence that propranolol may reduce the rise in central blood volume and central venous pressure in response to a saline load in hypertensive patients. The impairment of cardiac output from salt loading may be due to reduced venous return, as a depression of myocardial contractility alone would be expected to increase venous pressure. McSorley & Warren (1978) found that propranolol (a non-selective blocker) significantly reduced both skin blood flow and skin temperature in normotensive and hypertensive men at rest and during 2 minutes of cycle exercise in thermoneutral conditions but that metoprolol (a β -1 selective blocker) did not. It therefore seems possible that while non-selective beta blockers may contribute to a decreased skin blood flow and sweating response during thermal stress, as demonstrated in the studies listed below, β blockers selective for β -1 adrenoceptors may alleviate this problem.

Studies Involving Beta Blockade and Exercise

Beta blockers are commonly prescribed for patients with chronic heart disease and hypertension. Aerobic exercise is also recommended for this population (Seals et al., 1997; Sleight, 1996), however, information also exists which suggests that β blockers may be counterproductive to exercise performance and/or heat tolerance (Gordon et al., 1985). Ades, Gunther, Meacham, & LeWinter (1988) found that the blood pressure lowering effects of an aerobic program were abolished by therapy with propranolol (a non-selective β blocker) in the 30 hypertensive male and female subjects who participated in the 10 week exercise program. Furthermore, not only did drug therapy with propranolol limit aerobic conditioning (in terms of VO_2 max), but when drug therapy was

discontinued, blood pressure returned to the original hypertensive level. Metoprolol (a β -1 selective blocker) did not have the same detrimental effects (Ades et al., 1988). Sable, Brammell, Sheehan, Nies, Gerber, & Horowitz (1982) determined that non-hypertensive males (aged 21 to 35) also experienced little or no cardiovascular conditioning during a five week training period in conjunction with propranolol therapy.

Available studies tend to suggest that beta blocker usage (like ageing) may have detrimental effects on thermoregulation responses during exercise in the heat. Of those studies that obtained skin blood flow measurements, all found decreases in FBF with beta blocker usage (McSorley & Warren, 1978; Pescatello et al., 1987; Pescatello et al., 1990). The extent to which FBF was reduced in these studies depended upon whether selective or non-selective drugs were used and whether normotensive or hypertensive subjects were recruited to participate. For example, McSorley & Warren (1978) determined that both normotensive and hypertensive subjects experienced similar decreases in muscle blood flow with either selective (metoprolol) or non-selective (propranolol) usage. However, while both selective and non-selective drugs produced decreases in skin blood flow in hypertensive subjects, only the non-selective medication produced decreases in skin blood in normotensive subjects. The mildly hypertensive subjects utilized in another study (Pescatello et al., 1990) also experienced decreases in FBF with pindolol (a non-selective beta blocker) and metoprolol. However, it was noted that while normotensive men had significantly greater heat storage after 15 minutes of exercise in a thermoneutral environment, mildly hypertensive men had significant heat storage after 30 minutes of exercise.

Variations in temperature also produce similar results. Pescatello et al. (1987) found that 40 minutes of cycle exercise at 60% VO_2 max produced decreased in FBF and an attenuation of the FBF-Tes slope at 22°C and 32°C. In studies also measuring whether a decrease in FBF translated into increases in heat storage, Pescatello et al. (1987 & 1990) determined that beta blocker usage indeed

resulted in an increase in T_{es} during exercise and heat stress.

Of the two studies obtained for this review measuring sweat rate, one found decreases in sweat rate and the mean sweat - T_{es} relationship (Mack et al., 1986) and one found an increase in sweat loss with propranolol use (Gordon et al., 1985). Decreases in sweat rate translated into an increase in T_{es} and a decrease in T_{sk} for Mack et al. (1986), but no changes in T_{re} or T_{sk} were evident in the other investigation (Gordon et al., 1985). Pescatello et al. (1987) reasoned that the stable rectal temperature (T_{re}) and increased sweat rate encountered by Gordon et al. (1985) may have been due to the reduction in splanchnic flow during exercise, and that T_{re} may not have been an adequate reflection of internal body temperature under those conditions.

The mechanisms by which beta blockers act on the body during exercise and heat stress to produce decreases in FBF and potential decreases in sweat rate are not fully understood but Pescatello et al. (1987) suggested that β -1 and β -2 blockade elevated plasma catecholamine levels, possibly by augmenting α -vasoconstriction of the skin. Therefore, the attenuated slope of the FBF- T_{es} relationship during propranolol exposure may have been due to enhanced α -vasoconstriction. It is also possible that relative cutaneous vasoconstriction was stimulated by a baroreflex during β blockade. Decreased arterial pressures, systolic, and or pulse pressure would decrease stimulation of the sinoaortic baroreceptors and reflexly act to increase vascular resistance in nonessential beds, therefore shifting blood centrally.

During exercise, stroke volume increased (with β blockers) and fully compensated for the decreased heart rate to maintain cardiac output. Pescatello et al. (1987) reasoned that the six males used in this study were physically fit and that those in worse physical conditioning may not have been able to maintain cardiac output (due to the inability to increase stroke volume when heart rate decreases). Therefore, since cardiac output was not altered by propranolol, the decreased core-to-skin heat flux with β blocker usage could not have been attributed to a diminished cardiac output as

suggested by Gordon et al. (1985).

Pescatello et al. (1990) concluded that the non-selective β blocker had similar effects on forearm blood flow between normotensive and hypertensive men. However, the absolute decrease in heat transfer with non-selective β blockers was smaller in hypertensives than in normotensives. Hypertensives have been shown to have a lower cardiac output than normotensives during mild exercise in the heat. Individuals who are unable to raise cardiac output during exercise must rely on a redistribution of blood flow from splanchnic and cutaneous vascular beds to the active muscles to meet the oxygen delivery requirements. Hypertensive individuals may be unable to increase stroke volume to a sufficient extent to compensate for the reduction in heart rate during β blockade. Despite the tendency for a greater heat retention with non-selective β blockers, hypertensive individuals showed only a slight elevation in T_{es} with respect to placebo conditions. Differences may have become detectable with time or an increased sample size, but the inability to demonstrate significance in the protocol may have also been the result of the relatively low FBF response to body heating in hypertensives. The reduction in the M_{sw} - T_{es} relationship without alteration in the T_{es} threshold for sweating after β blockade suggested to Mack et al. (1986) that the influence of propranolol on M_{sw} was mediated at the level of the sweat gland. Beta blockers may have also reduced the small influence of the catecholamines on sweating. It was concluded that the reduction in sweating at any given T_{es} during beta blockade was partially caused by a reduction in peripheral input to the central integrator, itself the consequence of an altered peripheral vascular response and partially caused by the direct effect of β blockade on the sweat gland (Mack et al., 1986).

Gordon & Duncan (1991) noted that β blockers may result in increased susceptibility to exertional heat injury via an impairment in skin blood flow secondary to a reduction in cardiac output and or unopposed α -adrenergically mediated vasoconstriction. Non-selective β blockers may increase the risk for dehydration and hyperthermia and, by implication, their adverse physiological effects

during exercise (Gordon & Duncan, 1991).

Table 2-1
Studies Involving Older Men And Temperature Regulation

AUTHOR	SUBJECT	TYPE OF HEATING	EFFECTS OF AGE ON SWEATING	EFFECTS OF AGE ON BLOOD FLOW	EFFECTS ON BODY TEMP
Sagawa et al., 1988	*older men n = 6 (61-71yrs) *younger men n = 10 (21-39yrs)	passive - seated in chamber for 130min	no difference in SR	FBF lower in older men	Tes at onset of sweating greater in older men
Buono et al., 1991	*older men n = 10 trained (68 ± 3yrs) *older men n = 10 untrained (72 ± 2yrs) *younger men n = 10 trained (27 ± 1yrs) *younger men n = 10 untrained (28 ± 2yrs)	passive - sweating induced	↓SR in older men, but trained men showed less of a decrease	—	—
Inoue et al., 1991	*older men n = 10 (60-71yrs) *younger men n = 9 (20-25yrs) -all "healthy"	passive - 60min seated in chamber: 35°C, 45%RH	slight ↓SR in older men but not significant	—	↑Tre in older men
Tankersley et al., 1991	*older men n = 7 highly fit *older men n = 6 normally fit (58-74yrs) *younger men n = 7 normally fit (24-32yrs)	20min test (treadmill) at 65%VO ₂ max in a warm, humid env: 30°C, 50-60%RH	SR of highly trained older men intermediate to other two groups	FBF of highly trained older men intermediate to other two groups	—
Armstrong & Kenney, 1993	*older men n = 6 (58-67yrs) *younger men n = 6 (22-31yrs)	passive - 2hrs with an ↑ in temp from 28°C to 46°C RH = 28% to 11% (at 46°C)	*↑ in steady state SRchest over final 30min in younger men *lowering of Tb threshold for onset of sweating in both groups after acclimation	FBF-Tb relationship lower in older group (before & after acclimation)	no age difference in Tsk, Tre, or Tb
Kenney & Ho, 1995	*older men n = 6 (59-71yrs)(O) *younger men n = 6 (20-32yrs)(Y)	passive - 50 min cycling -20 min at 35% VO ₂ peak & 30 min at 60% VO ₂ peak *one trial at 22°C *one trial at 36°C	—	at both temps:FBF ↑ larger in Y. *less BF was moved away from renal & splanchnic areas in O.	↑Tsk in Y during ex.at 60% VO ₂ peak, ↑Tes in Y during ex.at 60% VO ₂ peak

LEGEND:

SR: Sweat Rate
 FBF: Forearm Blood Flow
 Tb: Body Temperature
 Tsk: Skin Temperature
 —: No Data

Msw: Steady State Sweat Rate
 ABF: Arm Blood Flow
 Tes: Oesophageal Temperature

Table 2-2
Studies Involving Older Women And Temperature Regulation

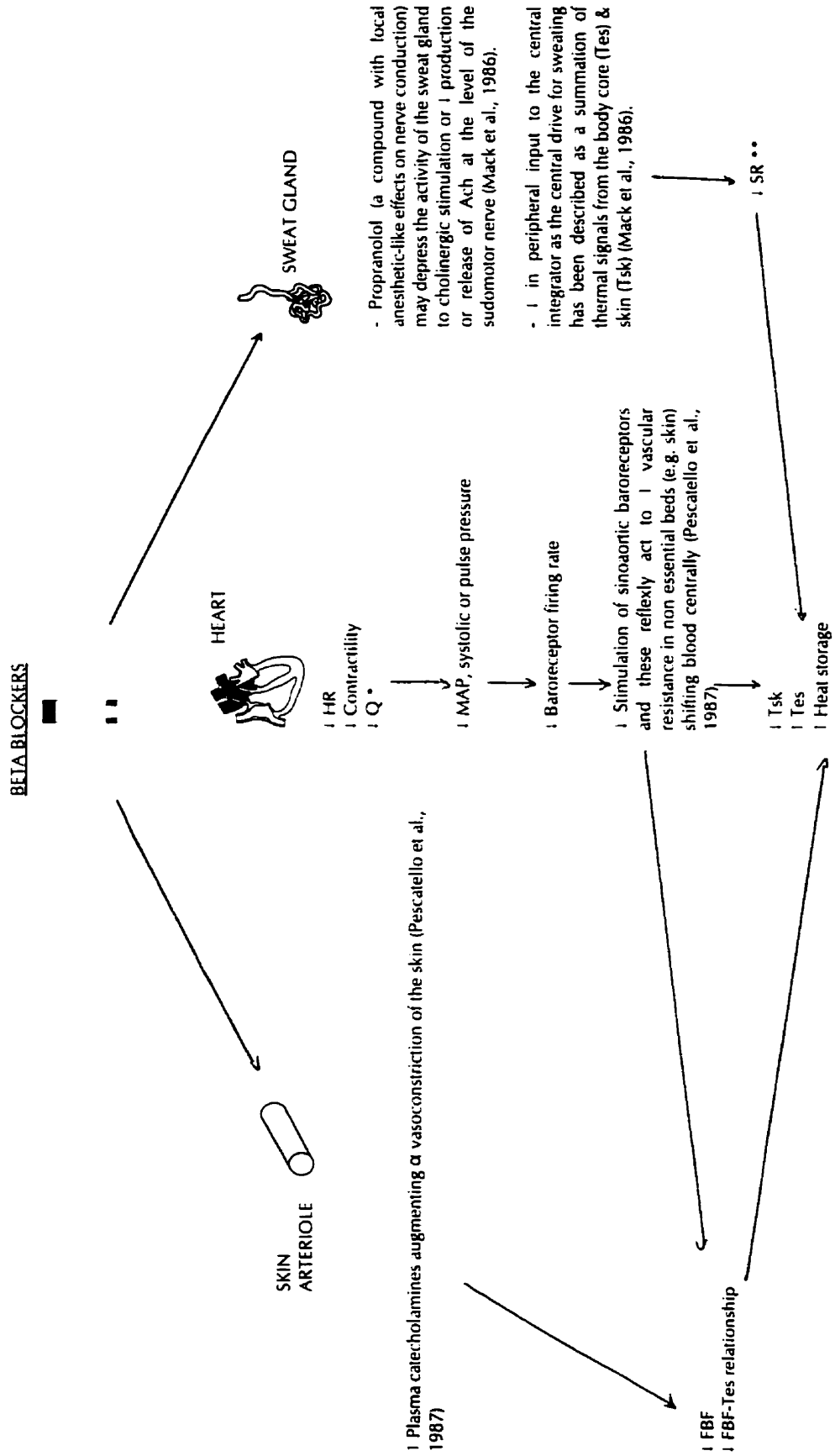
AUTHOR	SUBJECT	TYPE OF HEATING	EFFECTS OF AGE ON SWEATING	EFFECTS OF AGE ON BLOOD FLOW	EFFECTS ON BODY TEMP
Drinkwater et al., 1982	*older women n = 10 (57.7 ± 1.9yrs) *younger women n = 10 (38.4 ± 2.1yrs)	passive - 120min at 40°C, RH = 45%	no difference in SR, onset of sweating, or regional SR between groups	-	no age difference in Tre or Tsk
Anderson & Kenney, 1987	*older women n = 8 (52-62yrs) *younger women n = 8 (20-30yrs)	2hr treadmill walk at 35-40% VO2max Tdb = 48°C Twb = 25°C RH = 15%	SR in older women	-	Tre in older women
Kenney, 1988	*older women n = 4 *older men n = 2 -all 55+ *Younger women n = 4 *Younger men n = 2 -all 19-30yrs	75min cycle ergometer ride at 40% VO2max Tdb = 37°C Twb = 30°C RH = 60%	no difference in SR between groups	*↑ FBF(& Q) in younger groups during exercise but not at rest *slope of ABF-Tre relationship for vasodilation attenuated in older groups (but Tre threshold was not different)	no difference in Tre or Tsk

Table 2-3
Studies Involving Beta Blockers And Temperature Regulation

AUTHOR	SUBJECT	PROTOCOL	EFFECTS ON SWEATING	EFFECTS ON BLOOD FLOW	CORE TEMP
McSorley & Warren, 1978	*men n = 10 (healthy) *men n = 4 (hypertensive)	*2min of cycle exercise at 40% of maximum tolerated load *passive - 20min seated at 23-24°C after cycle exercise	-	* ↓ skinBF with propranolol but not metoprolol in normotensives * ↓ muscleBF with propranolol and metoprolol * both propranolol and metoprolol ↓ SkinBF in hypertensives * similar muscleBf results as with normotensives	-
Gordon et al., 1985	*men n = 11 (19.9yrs) "healthy"	2hrs of block stepping in the heat Tdb = 33°C Twb = 31°C *at a work rate of 54 W	↓ sweat loss with propranolol (not atenolol)	-	Tre & Tsk not significantly altered with either compound
Mack et al., 1986	*men n = 6 (32 ± 6yrs) "healthy"	40min of cycle exercise at 60% VO2max	* ↓ SR * ↓ Msw-Tes relationship	-	* ↓ Tes & ↓ Tsk * Tes threshold for sweating unaltered
Pescatello et al., 1987	*men n = 6 (31.7 ± 6.2yrs) "healthy"	40min of cycle exercise at 60% VO2max (at 22°C OR 32°C) *4 tests	-	↓ FBF at both temperatures * ↓ FBF-Tes slope at both temps with propranolol	↓ Tes at both temperatures
Pescatello et al., 1990	*men n = 6 (42yrs) -mildly hypertensive but not on medication	30min of cycle exercise at 60% VO2max at 22°C < 51% RH -no forced air movement	-	↓ FBF with pindolol and metoprolol	↓ Tes with pindolol

NOTE: IN ALL EXPERIMENTS, HEART RATE WAS LOWERED SIGNIFICANTLY BY MEDICATION

FIGURE 2-2 Summary of The Effects of β -Blockage on Thermoregulatory Responses



- Propranolol (a compound with local anesthetic-like effects on nerve conduction) may depress the activity of the sweat gland to cholinergic stimulation or ↓ production or release of ACh at the level of the sudomotor nerve (Mack et al., 1986).

- ↓ in peripheral input to the central integrator as the central drive for sweating has been described as a summation of thermal signals from the body core (Tes) & skin (Tsk) (Mack et al., 1986).

↓ Plasma catecholamines augmenting α vasoconstriction of the skin (Pescatello et al., 1987)

* Q was not altered in Pescatello et al. (1987) study. Therefore ↓ core-to-skin heat flux with propranolol cannot be attributed to diminished Q (as suggested by Gordon et al., 1985).

** ↓ SR was not found by Gordon et al., (1985)

MENOPAUSE AND THERMOREGULATION

Menopause has been defined as the permanent cessation of menstruation, and is assumed to have occurred following a period of amenorrhea for 12 months (Khaw, 1992). The average age of menopause in most Western industrialized countries is 50 years, although a wide range has been quoted between 35 to 59 years (Khaw, 1992; Al-Azzawi, 1992). Premenopausally, the ovary is the major source of circulating estrogens (especially oestradiol). After menopause, the major source of estrogens is from peripheral conversion in adipose tissue of adrenal androgen precursors (especially androstenedione) to estrogens, mainly estrone. The amount of body fat is therefore a major determinant of estrogen levels in postmenopausal women (Khaw, 1992). Some of the symptoms associated with menopause are hot flushes, night sweats, palpitations and headaches. All of these are attributed to vasomotor instability (Khaw, 1992). Psychological problems include depression, insomnia and tiredness. Other effects noted are vaginal dryness, atrophic vaginitis and dyspareunia (Khaw, 1992).

Effects of Estrogen on Thermoregulation

Studies have suggested that estrogen may be beneficial to thermoregulatory responses such as sweating and cutaneous vasodilation. An increase in plasma estrogen levels may act centrally to lower the set point about which core temperature is regulated at rest and during exercise (Tankersley et al., 1992; Carpenter & Nunneley, 1988; Hessemer & Bruck, 1985). Carpenter and Nunneley (1988) found that despite similar sweat evaporation during heat tests, body temperatures were significantly lower at ovulation (when oestrogen, follicle stimulating hormone and luteinizing hormone are high) and higher during the luteal phase. Thresholds for sweating, shivering, and cutaneous vasodilation also increase in the luteal phase compared with the follicular phase (Hessemer & Bruck, 1985). Baker et al. (1994) determined that estrogen treated rats had significantly higher rates of evaporative water loss and lower core temperatures during heat exposure than untreated animals.

Estrogen appears to have a beneficial effect on exercise during heat stress. Tankersley et al. (1992) found that estrogen replacement therapy resulted in a lower heart rate and core temperature (as demonstrated by a decrease in both T_{es} and T_{re}) at rest and during exercise in the heat. Additionally, sweat rate and arm blood flow are higher at any given core temperature after estrogen therapy due to a lower T_{es} threshold. The facilitating effects of estrogen on vasodilation and core temperature are demonstrated by other researchers (Brooks, Morgan, Pierzga, Wladkowski, O'Gorman, Derr & Kenney, 1997; Lieberman et al., 1994; Taddei, Viridis, Ghinadoni, Mattei, Sudano, Bernini, Pinto & Salvetti, 1996). Taddei et al. (1996) found that menopause affects endothelium-dependent vasodilation in both normotensive and hypertensive women. The men in this study showed declining endothelial responses during the third decade that were gradual and progressive until old age. In contrast, the women showed only slightly affected endothelium-dependent vasodilation up to the fifth decade. After 49 years of age (and after menopause), endothelium-dependent vasodilation showed a decline that was steeper than that in men (Taddei et al., 1996). Lieberman et al. (1994) suggested that estrogen improves endothelium-dependent vasodilation by increasing synthesis and release of nitric oxide, by inhibiting its degradation, or by altering the balance of vasodilator and vasoconstrictor prostaglandins.

Effects of Oestrogen on Cardiovascular Strain

Past data from experimental animals indicate that chronic administration of oestrogen produces hemodynamic and cardiac changes in non-pregnant animals similar to those in pregnancy (Veille, Morton, Burry, Nemeth & Speroff, 1986). Results reveal an increase in cardiac output (due to an increase in stroke volume) in infertile women during oestrogen induction. However, since blood volume was not measured in this study, it could not be determined whether the increased end diastolic volume was due to a remodelling of the heart (as in pregnancy) and during oestrogen administration, or simply to increased filling. No changes in heart rate or MAP were noted in this study but it must be

noted that there was no heat or exercise strain. A more recent study did not share the same finding. During a treadmill max test Lee et al. (1997) found no differences in heart rate, blood pressure, double product, exercise duration, or ST-segment configuration between treatment or no treatment for one month. These researches did note however that failure to support their hypothesis may have been due in part to the usage of a less potent estrogen substance than that used in previous studies.

Effects of Estrogen on Body Fluids

In addition to the direct effects on the central temperature controller in the brain, it has been suggested that the influence of estrogen could also be related to changes in the osmolarity or volume of body fluids (Baker et al., 1994). Blahd, Lederer & Tyler (1974) studied the effects of oral contraceptives on body water and electrolytes. Increased body water, intracellular water and decreased Cl^- is assumed to be related to changes in water occurring at the time of ovulation. This is believed to be associated with an increase in body sodium that may be estrogen induced. Oral contraception resulted in much less fluctuation in body water during the menstrual cycle than controls because estrogen and or progesterone levels remain high (Blahd et al., 1974). It was also noted by this study that although rare, some women experienced significant levels of sodium retention and that these changes might have compromised the buffer capacity of the renin-angiotensin-aldosterone system. Therefore, benefits of estrogen to the thermoregulatory system during heat stress could also be related to estrogen-induced changes in the osmolarity or volume of body fluids. In many species, the rate of thermoregulatory evaporation in warm environments is reduced when plasma or cerebrospinal fluid osmolarity is increased by dehydration or by administration of hypertonic fluids (Baker et al., 1994).

Summary

Estrogen may improve thermoregulation through a direct effect on the temperature controller (Tankersley et al., 1992; Baker et al., 1994; Carpenter & Nunneley, 1988; Hessemer &

Bruck, 1985), and through effects on blood vessels themselves (Lieberman et al., 1994). Estrogen has also been shown to have positive effects on the regulation of body fluids (Blaht et al., 1974; Baker et al., 1994), and on the cardiovascular system (Vielle et al., 1986) although results are controversial (Lee et al., 1997). It should be noted that all of these situations could potentially produce beneficial effects for women during exercise and heat stress. Therefore, postmenopausal women not on hormonal replacement therapy might be expected to be at a disadvantage with reduced estrogen levels, as well as the other effects of ageing on the thermoregulatory system mentioned earlier. Unfortunately, at this time the argument between whether ageing per se or estrogen is responsible for the detrimental effects on the thermoregulatory system in elderly women has not been determined.

**SUMMARY: MENOPAUSE AND IMPLICATIONS REGARDING EXERCISE AND
THERMOREGULATION**

Studies involving thermoregulation and the post-menopausal woman shed some light concerning the effects of heat and exercise on the older adult. The literature suggests (as demonstrated in Table 2-1, Table 2-2 and Figure 2-2) that older individuals (55+) tend to have a decreased sweat rate (Inoue et al., 1991; Tankersley et al., 1991; Armstrong & Kenney, 1993; Anderson & Kenney, 1987), although this is not a universal finding (Drinkwater et al., 1982; Sagawa et al., 1988; Kenney, 1988). It should be noted that those studies in which no differences in sweat rate between younger and older individuals were found tended to take place in more humid settings (Kenney, 1988; Drinkwater et al., 1982) where sweat rate may have been more likely to be decreased in all individuals, due to the ineffectiveness of sweating in such conditions.

Additionally, some studies have also found that blood flow is likely to be decreased in older individuals (Tankersley et al., 1991; Armstrong & Kenney, 1993; Sagawa et al., 1988; Kenney, 1988). Of the studies reviewed here, only two specifically involved post-menopausal women and exercise heat strain (Kenney 1988; Anderson & Kenney, 1987). One found that while exercising in dry heat conditions, older women experienced a decrease in sweat rate which translated into an increase in heat storage (Anderson & Kenney, 1987). Kenney (1988) found that while there was a decrease in cardiac output and arm blood flow in elderly women, as well as an attenuation of the arm BF-Tre relationship, sweat rate, Tre and Tsk were not affected. It is possible (as mentioned above) that the higher humidity involved in this experiment may have contributed to the results.

Since no studies could be found involving the thermoregulation of post-menopausal women and β blocker usage those studies used in this review included results found on males. The studies available also tended to use younger to middle aged men, with the oldest sample approximately 42 years of age (Pescatello et al., 1990). While the decrease in heart rate and FBF with β blocker usage

tended to be a universal finding, effects on sweat rate were divided. Mack et al. (1986) found a decrease in sweat rate and the M_{sw} - T_{es} relationship, while Gordon et al. (1985) found an increase in sweat loss with propranolol (not atenolol). In those studies where body temperature measurements were obtained, the decrease in FBF tended to result in an increase in heat storage (Pescatello et al., 1987; Pescatello et al., 1990; Mack et al., 1986). However Gordon et al. (1985) found no change in T_{re} and T_{sk} indicating the possibility that T_{re} may not be sensitive to β blocker usage. The decrease in sweat rate and FBF often noted in older individuals might be even more detrimental during administration of β blockers.

An increasing number of adults are living well into old age and often, prescription drug use is a reality. Due to the lack of information on the older female population, it seems apparent that further studies concerning the use of medication and exercise heat stress could provide some useful information.

CHAPTER THREE: METHODS AND PROCEDURES

Subject Selection and Screening

Seven post menopausal women volunteered for this study. Subjects were healthy as this study excluded those suffering from any heart, lung, or blood vessel disease as well as those with diabetes, high cholesterol or high blood pressure. Subject health questionnaires were included in all informed consent packages to eliminate those with potential contraindications to beta blocker medication. Also excluded were those on medications having any effect on temperature regulation such as hormonal replacement therapy and those suffering from chest pain, arthritis or other joint pain causing discomfort during extended cycle exercise. A physician screened participants using these medical histories, as well as a resting 12 lead electrocardiogram. This study had approval from the University of Manitoba's Human Ethics Committee, and all volunteers provided written informed consent. The results of two subjects are not included here due to technical difficulties with the climatic chamber, and one of these volunteers agreed to repeat the experiment. One additional woman was screened out during her initial test when her 12 lead electrocardiogram appeared abnormal. Data analysis was therefore carried out on five subjects.

Study Design

After determination of peak VO_2 on a cycle ergometer, all subjects were required to complete two 45 minute cycle bouts at 50% VO_2 peak in a climatic chamber set at 32°C, 30% relative humidity and minimal forced air movement. Two hours before both trials, either 80 mg of Propranolol (a non-selective beta blocker) or a suitable placebo was ingested. This experiment was double blinded and the order of the tests randomized, according to a balanced design, throughout the subject population. Therefore, all participants completed three cycle tests: a peak VO_2 test, a beta blocker trial in the heat and a placebo trial in the heat. All tests were conducted between September 1997 and May 1998, and

a physician was present for all tests. To analyze the differences between placebo and beta blocker treatments, paired t tests were used.

INSTRUMENTATION

Aural Canal Temperature

Aural canal temperature was monitored as an indicator of core temperature. A Mon-a-Therm tympanic thermocouple (Mallkinckrodt, St. Louis, MO) was inserted into the ear canal where it was situated close to the tympanic membrane. The probe was cushioned with a small amount of cotton which was taped to the outer ear to prevent movement of the probe. This, in turn, was held in place with an ear protection head set.

Skin Temperature

Twelve disks (approximately 2.5 cm in diameter) were taped to the skin at various sites on the body. Specifically, the sites included the forehead, left chest, right abdomen, right scapula, left lower back, right upper lower arm, right hand, left anterior thigh, right posterior thigh, right anterior calf, left posterior calf, and left foot. These disks gave an indication of the skin temperature as well as flow of heat to or from the skin at that point. Average skin temperature was calculated from a series of weighted factors from these 12 sites as described by Layton et al. (1983).

Data from the tympanic and skin thermocouples were obtained using an electrically isolated Macintosh IICI computer equipped with a NB-MIO-16L 16-channel analog-digital converter (National Instruments, Austin TX). At 30 second intervals, the results were averaged for the previous 30 second period, displayed graphically on the computer screen, and recorded in spreadsheet format on a hard disk. The process was controlled using LabVIEW 2 graphical signal processing software (National Instruments, Austin TX).

Skin Blood Flow

A Periflux PF2B laser doppler flowometer (LDF) (Perimed, Stockholm, Sweden) was used to monitor skin blood flow at the forearm. The probe was held in place on the forearm by a plastic disk. This disk, in turn, was affixed to the skin by an adhesive ring. The LDF probe was placed on the dorsal aspect of the right forearm, adjacent to the forearm skin temperature disk.

Sweat Rate

Sweating rate was monitored at the upper arm by a small capsule and dry air (of absolute humidity) was flushed through it at a fixed flow rate of 1 L/min. This flow was controlled by a Brooks 5850 Mass Flow Controller (Emerson Electric, Hatfield PA). The change in water content of the air was dependent on the sweating rate. The amount of water evaporated was calculated from the relative humidity change (RH) and temperature of the air as measured by an Omega HX93 Humidity and Temperature sensor (Omega Engineering, Stamford, CT). Sweat rate was obtained in $\text{g/m}^2/\text{hr}$.

Heart Rate

Heart rate was monitored continuously by a DC battery operated 43100A Defibrillator/ECG monitor (Hewlett-Packard). Two electrodes were attached to the skin with adhesive pads to the right and left shoulder (near the right and left midclavicular line respectively, directly below the clavicle). A third electrode was placed approximately between the 6th and 7th intercostal space on the left midclavicular line.

Blood Pressure

Blood pressure was measured with an automated Dinamap Adult/Pediatric Vital Signs monitor (Critikon Inc., Tampa, FL). Measurements were recorded every five minutes.

Oxygen Consumption

For three peak VO_2 tests, oxygen consumption was measured with a Beckman Metabolic Measurement Cart (MMC) (Beckman Instruments, Anaheim, CA). Subjects were connected to this

instrument via a headset with connecting face mask. The MMC was set up in the "average mode" and was programmed to record measurements at 30 second intervals. Expired air was conducted to a mixing chamber from which a small sample was diverted into two streams: one was dried while the other had both CO₂ and moisture removed from it. The streams were passed over heated wires arranged in a Wheatstone's bridge circuit. The rate at which heat was lost from the heated wires when they were exposed to inspired and expired gas was directly related to the flow rate across the wires (ventilation). These resistances operated on the principle of variable coefficients of thermal conductivity with O₂ and CO₂ concentrations being expressed as percentage differences from atmospheric air (Soares, Sheela, Kurpad, Kulkarni & Shetty, 1989). Peak VO₂ was calculated every 30 seconds from measurements of FEO₂, FECO₂ and minute ventilation (VE). After measurement of flow rate, the amounts of oxygen and carbon dioxide were determined using Beckman OM-11 and LB-2 analyzers for O₂ and CO₂ respectively (Beckman, Anaheim, CA), and this information was obtained from a data sheet printout from the cart. Calibration was done with gases of known concentration before each test.

For two peak VO₂ tests and all cycle heat tests, oxygen consumption was measured with a V_{MAX} 229 analyzer/pneumatics system (Sensor Medics, Yorba Linda, CA). This system is a combination of two modules (an analyzer module and a pneumatics module) which work in conjunction to analyze gas samples. Expired air from the subject was drawn into the pneumatics module which houses a 2.6 litre mixing chamber and a series of valves. Expired flow was measured directly using a mass flow sensor. This system used a pair of heated stainless steel wires (similar to the Beckman system) to measure gas flow. The air samples were then directed to the analyzer module where they were pulled through the paramagnetic O₂ and non-dispersive infrared thermopile CO₂ analyzers (Type BF, Sensor Medics, Yorba Linda, CA) for analysis. A large mass flow sensor board (located in the analyzer module)

was responsible for converting system signals from analog to digital to be displayed on the IBM computer screen. Gas and volume calibrations were done before each heat test.

Heat Tests

All cycle heat tests were conducted in a Conviron CMP 3244 climatic chamber (Winnipeg, MB).

PROCEDURES

Determination of peak $\dot{V}O_2$

A maximal cycle test was used to determine the peak $\dot{V}O_2$ of all subjects. Subjects pedalled on a cycle ergometer at a rate of 60rpm and a resistance of 0.5 kp. The exercise intensity was raised by increasing the resistance of the flywheel 0.5 kp (an increase in power output of 180 kpm/min) every two minutes (Certified Fitness Appraiser Laboratory Manual, 1991). Exercise intensity was increased until the subject could no longer continue (subjective exhaustion). Other criteria for exhaustion included a RER (respiratory exchange ratio) greater than or equal to 1.1, and achievement of age predicted maximal heart rate. The highest volume of oxygen obtained during the test was used as peak $\dot{V}O_2$. The Beckman MMC was used for O_2 consumption measurement for three peak $\dot{V}O_2$ tests. The $V_{MAX}229$ system was used in two tests.

A single lead ECG (CM5) was used to estimate heart rate. Heart rate was monitored continuously throughout the test, and recorded at the end of each two minute stage.

Anthropometric Data

All subjects had their height and weight determined as well as a series of skinfolds. The sum of seven skinfolds was used to predict body density. All measurements were taken on the right hand side of the body at the chest, axilla, triceps, subscapula, abdomen, suprailium and thigh as suggested by Jackson & Pollock (1985). The equation below, derived by Jackson & Pollock (1980) was tested on

a large population of women varying greatly in age and body composition type and should therefore have been suitable for the subjects tested in this investigation.

$$\text{Body Density} = 1.1470 - 0.00042930 (X_1) + 0.00000065 (X_1)^2 \\ - 0.00009975 (X_4) - 0.00062415 (X_5)$$

Where: X_1 = Sum of all seven skinfolds

X_4 = Age

X_5 = Gluteal circumference

(Jackson & Pollock, 1980)

Percentage body fat was determined by the Siri equation:

$$\text{Body Fat (\%)} = (495/\text{Body Density}) - 450$$

(Siri, 1956)

Body Mass Index (BMI) was also be calculated.

$$\text{BMI} = \text{weight}/\text{height}^2 = \text{kg}/\text{m}^2$$

Cycle/Heat Protocol

All experiments were conducted at the same time of day for each subject to avoid daily fluctuations in body temperature. Subjects were asked to abstain from food and drink (including caffeinated beverages) for at least two hours prior to arriving at the lab. They were also asked not drink any beverage containing alcohol nor to partake in any strenuous physical activity for six hours before the tests. All participants completed two exercise/heat tests. Two hours before each trial, the subject ingested either 80 mg of Propranolol (a non-selective beta adrenergic blocker) or a suitable placebo.

Testing took place at the University of Manitoba Environmental Studies Laboratory in the Max Bell Centre. Both tests were performed in a climatic chamber at an ambient temperature of 32.0 ± 0.1 °C, 31.8 ± 1.1 % relative humidity and minimal forced air movement. Subjects reported to the lab wearing either a fitted bathing suit and shorts, or a sleeveless tanktop and shorts, and sat for at least 30 minutes while all of the equipment was initiated. Each test was preceded by a 15 minute baseline control in the heat. All participants completed 45 minutes of cycle exercise at 50% VO_2 peak (as determined from previous maximal testing), followed by 15 minutes of passive recovery in the heat. Measurements included tympanic temperature, average skin temperature, skin blood flow, sweating rate, heart rate and blood pressure.

DATA ANALYSIS

There was one independent or treatment variable (medication) with two levels (beta blocker vs. placebo). Dependent variables included aural canal temperature, skin temperature, skin blood flow, sweating rate, heart rate and blood pressure. To analyse the differences in the dependent variables between placebo and beta blocker treatments, paired t tests were used. For all tests of significance, alpha (α) was set at 0.05. Analyses for all dependent variables incorporated the results of five subjects, excluding sweat rate, where, due to technical difficulties with the sweat rate monitor, the results of only three subjects were used.

Regression analyses were conducted to examine relationships between selected dependent variables including: 1) aural canal temperature (T_{AC}), 2) average skin temperature (T_{SKavg}) and 3) skin blood flow (SKBF) and independent variables. The amount of change in these dependent variables was compared to independent variables including: 1) the difference in baseline SBP between placebo and drug trials; 2) the difference in baseline heart rate between placebo and drug trials; 3) age; 4) number of years post menopause; 5) weight; 6) percentage body fat (%fat) and 7) peak VO_2 . To examine the responsiveness to propranolol, additional regression analyses were conducted comparing:

1) the difference in baseline SBP between placebo and drug trials and 2) the difference in baseline HR between placebo and drug trials (dependent variables) to the resting SBP (independent variable).

CHAPTER FOUR: RESULTS

Subject Characteristics

The women who participated in this study were physically active on a regular basis. Four of the volunteers were recreational athletes, and popular activities included cycling, walking and hiking. The fifth was a competitive triathlete and a recent Boston Marathon participant. One volunteer was a light smoker. Subject characteristics are presented in Table 4-1.

Since all five women completed both trials results are presented for all five subjects, and sweat rate data is available for only three subjects. Comments about the trials were encouraged and although three of the women could notice neither physical nor perceived exertion differences between the trials, two women did make some assertions. One subject correctly noticed a faster beating heart during one trial and another subject believed she was sweating harder through one test when in fact she was not.

Aural Canal Temperature

Aural canal temperature (T_{AC}) was similar during both trials until approximately minute 36 (21 minutes of exercise) (Figure 4-1). Thereafter the T_{AC} during the propranolol trial began to increase at a slightly faster rate. The change in aural canal temperature (ΔT_{AC}) as a result of 45 minutes of cycling was 1.19 ± 0.30 °C and 1.62 ± 0.49 °C for placebo and propranolol treatments respectively ($p < 0.05$). There were no significant differences between trials during baseline, at 15, 30 or 40 minutes of exercise nor during recovery. Although it was not statistically significant, there was a slight variation in the time to peak T_{AC} . During the placebo trial, T_{AC} started to decrease immediately upon cycling cessation. The time to peak T_{AC} during this test was 59.5 ± 3.3 minutes (the end of exercise). During the propranolol trial, T_{AC} continued to rise for an additional two minutes. The time to peak T_{AC} was 62.1 ± 3.3 minutes. A comparison of the T_{AC} response during placebo and propranolol trials between two subjects is presented in Figure 4-5.

Average Skin Temperature

Average skin temperature (T_{SKavg}) rose 1.08 ± 0.50 °C and 0.77 ± 0.41 °C as a result of 45 minutes of exercise during placebo and propranolol trials respectively ($p < 0.05$) (Figure 4-2). Average skin temperature was similar to T_{AC} in that there were no significant differences between trials at 15, 30 or 40 min of exercise. T_{SKavg} did not demonstrate signs of propranolol depression until approximately minute 52 (37 minutes of cycle exercise). During the 15 minute recovery period, placebo T_{SKavg} fell 0.52 ± 0.23 °C and propranolol T_{SKavg} decreased 0.30 ± 0.11 °C ($p < 0.05$).

Skin Blood Flow

Although blood flow during the propranolol trial was slightly depressed compared to the placebo trial, the overall change was not significant (Figure 4-3). The SKBF change during exercise was 1.40 ± 0.83 V and 1.13 ± 0.55 V for placebo and propranolol treatments respectively. There were no significant differences between trials during baseline, exercise or recovery.

Sweat Rate

The increase in sweat rate (SR) during the two trials showed similar patterns in response to cycling exercise (Figure 4-4). There were no significant differences in SR between placebo and propranolol trials at any time during baseline, exercise or recovery.

Heart Rate and Blood Pressure

Baseline heart rate values were not significantly different between trials, however, heart rate was significantly depressed ($p < 0.05$) with propranolol at 30 and 40 minutes of exercise (Table 4-2). The average exercise heart rates during placebo and propranolol trials were 113 ± 26 beats per minute (bpm) and 93 ± 14 bpm respectively ($p < 0.05$). Heart rate increased 56 ± 23 bpm above baseline during the placebo trial, and 37 ± 13 bpm during the propranolol trial ($p < 0.05$). At the end of the

recovery period heart rate was still significantly depressed during the propranolol trial compared to the placebo trial (66 ± 8 bpm and 85 ± 10 bpm respectively).

With one exception, blood pressure values were not significantly depressed by propranolol. Exercise measurements were not used because constant body movement often produced erratic changes in blood pressure readings. Baseline systolic blood pressure (SBP) did not differ significantly between placebo and propranolol trials, nor did diastolic blood pressure (DBP). However, SBP was significantly depressed with propranolol during recovery ($p < 0.05$). Recovery DBP was not significantly different between treatments (Table 4-2).

REGRESSION ANALYSIS

Response to Beta Blockers

A significant, positive relationship was identified between resting SBP and the change in baseline SBP between placebo and propranolol trials ($p < 0.05$) (Figure 4-6). Specifically, the higher the resting SBP, the larger the difference between baseline propranolol and placebo SBP ($R = 0.876$). A non-significant, positive relationship existed between resting SBP and the change in baseline HR between placebo and propranolol trials ($R = 0.852$).

The Effect of Response to Beta Blockers on Temperature Regulation

Regression analysis revealed non-significant, positive relationships between 1) the change in T_{AC} and the change in baseline SBP between placebo and propranolol trials, 2) the change in T_{AC} and the change in baseline HR between placebo and propranolol trials and 3) the change in T_{SKavg} and the change in baseline HR between placebo and propranolol trials. Negative relationships between 1) the change in T_{SKavg} and the change in baseline SBP between placebo and propranolol trials, 2) the change in SKBF and the change in baseline SBP between placebo and propranolol trials and 3) the change in SKBF and the change in baseline HR between placebo and propranolol trials were also not significant (Table 4-4).

The Effect of Age and Number of Years Post Menopause on Temperature Regulation

Positive relationships between 1) the change in $T_{SK_{avg}}$ and age and 2) the change in $T_{SK_{avg}}$ and the number of years post menopause and negative relationships between 1) the change in T_{AC} and age, 2) the change in T_{AC} and the number of years post menopause, 3) the change in SKBF and age and 4) the change in SKBF and the number of years post menopause were not significant (Table 4-4).

The Effect of Body Composition and Aerobic Power on Temperature Regulation

Regression revealed non-significant, positive relationships between 1) the change in $T_{SK_{avg}}$ and percent body fat (Figure 4-7) and 2) the change in T_{AC} and weight relationships, as well as non-significant, negative relationships between 1) the change in T_{AC} and percent body fat, 2) the change in T_{AC} and peak VO_2 , 3) the change in $T_{SK_{avg}}$ and weight, 4) the change in $T_{SK_{avg}}$ and peak VO_2 , 5) the change in SKBF and weight, 6) the change in SKBF and percent body fat and 7) the change in SKBF and peak VO_2 (Table 4-4).

TABLE 4-1. Subject Characteristics

Subject	Age (years)	Height (cm)	Weight (kg)	Body Fat (%)	Peak VO ₂ (ml/kg/min)	Yrs. Post Menopause	Resting HR (bpm)	Resting BP (mmHg)
1	51.8	163.8	61.1	32.6	25.0	2.3	60	118/67
2	59.3	168.9	88.5	34.1	19.0	10.0	71	110/70
3	58.5	167.6	71.6	27.9	40.6	12.3	51	124/77
4	64.2	161.0	65.4	32.7	27.0	11.4	75	110/70
5	59.5	162.6	54.4	25.5	27.4	12.0	57	106/62
Mean	58.7	164.8	68.2	30.6	27.8	9.6	62	113/69
SD	4.4	3.4	12.9	3.7	7.9	4.2	9	7/5

SD - Standard Deviation

Resting HR and BP values are those measured during initial 12 lead ECG / screening session.

TABLE 4-2. Average Heart rate and blood pressure response ($\bar{x} \pm SD$)

	Baseline	15 min of exercise	30 min of exercise	40 min of exercise	End of Recovery
Heart Rate (bpm)					
Placebo	67 ± 6	108 ± 27	118 ± 27	120 ± 27	85 ± 10
Drug	60 ± 7	93 ± 13	95 ± 16 *	93 ± 14 *	66 ± 8 *
Systolic BP (mmHg)					
Placebo	112 ± 10	N/D	N/D	N/D	96 ± 21
Drug	104 ± 12	N/D	N/D	N/D	89 ± 19 *
Diastolic BP (mmHg)					
Placebo	73 ± 15	N/D	N/D	N/D	67 ± 8
Drug	71 ± 8	N/D	N/D	N/D	61 ± 15

* - indicates significance between placebo and drug trials

N/D - indicates no data

TABLE 4-3. Comparison of heart rate and systolic blood pressure response

Subject	Resting BP (mmHg)	Baseline Pl BP (mmHg)	Baseline Pr BP (mmHg)	Δ Baseline SBP (Pr SBP - Pl SBP)	Δ Baseline HR (Pr HR - Pl HR)
1	118/67	126/92	120/70	-6	-16
2	110/70	106/56	101/71	-5	-4
3	124/77	121/87	103/67	-18	-13
4	110/70	105/72	99/73	-6	-1
5	106/62	104/60	101/75	-3	-3

Note: Resting BP refers to values taken during initial 12 lead ECG / screening session

Pr = Propranolol

Pl = Placebo

TABLE 4-4. R values for linear regressions

Dependent Variables	Independent Variables						
	Δ baseline SBP	Δ baseline HR	Age (yrs)	No. Of yrs Post Menopause	Weight (kg)	Body fat (%)	Peak VO ₂ (ml/kg/min)
Δ Tac	0.712	0.620	0.429	0.015	0.522	0.085	0.416
Δ TSKavg	0.037	0.503	0.508	0.754	0.457	0.859	0.352
Δ SKBF	0.103	0.183	0.345	0.103	0.375	0.304	0.035

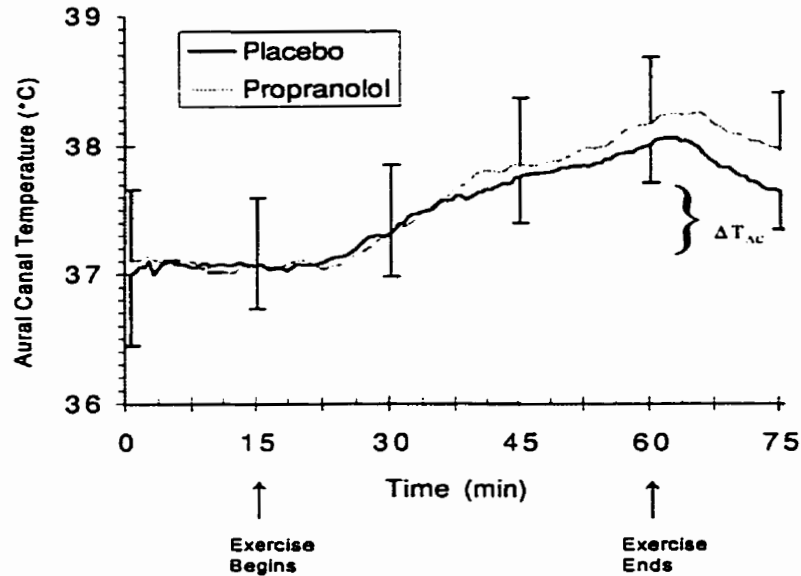


Figure 4-1. Aural canal temperature (T_{AC}) during baseline, exercise and recovery in placebo and propranolol trials ($n = 5$).

$\} \Delta T_{AC}$ - denotes a significant increase in T_{AC} in the propranolol trial compared to the placebo trial during 45 minutes of cycling exercise.

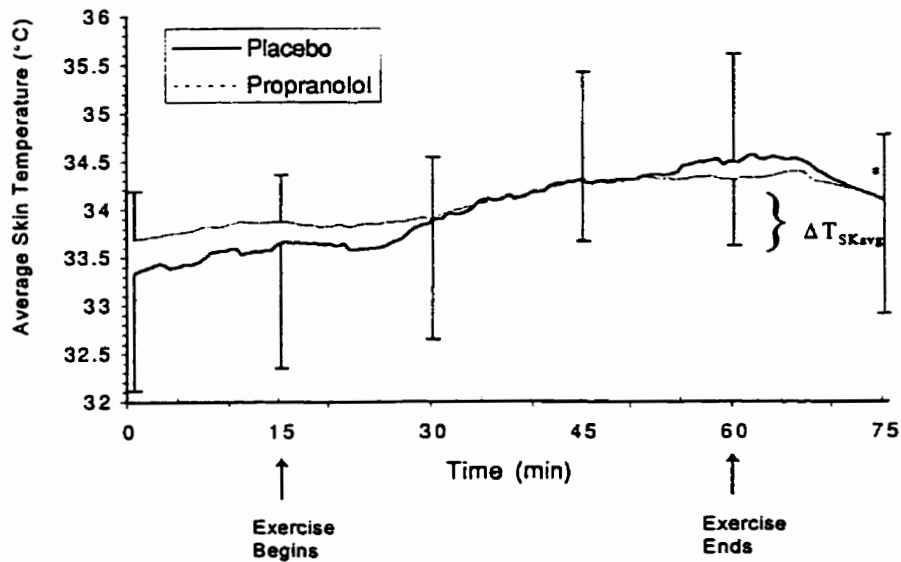


Figure 4-2. Average skin temperature (T_{SKavg}) during baseline, exercise and recovery in placebo and propranolol trials ($n = 5$).

$\} \Delta T_{SKavg}$ - denotes a significant increase in T_{SKavg} in the placebo trial compared to the propranolol trial during 45 minutes of cycling exercise and a significant decrease in T_{SKavg} in the placebo trial compared to the propranolol trial during recovery (*).

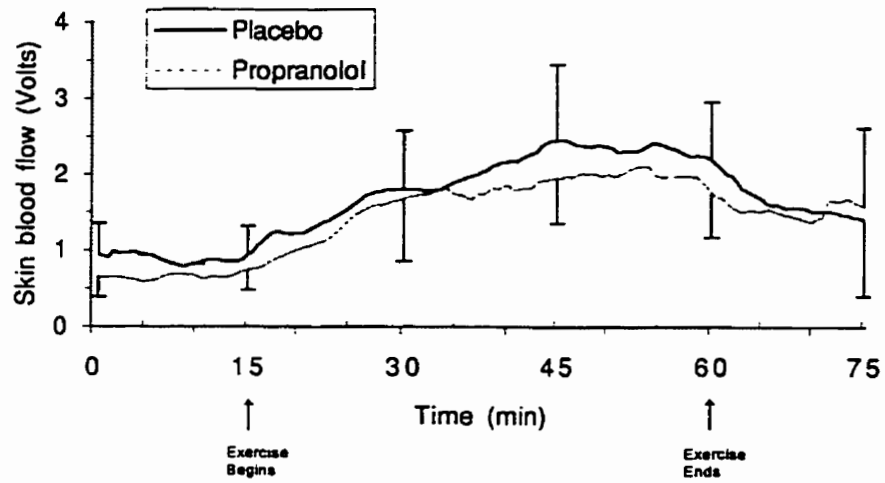


Figure 4-3. Skin blood flow (SKBF) during baseline, exercise and recovery in placebo and propranolol trials (n = 5).

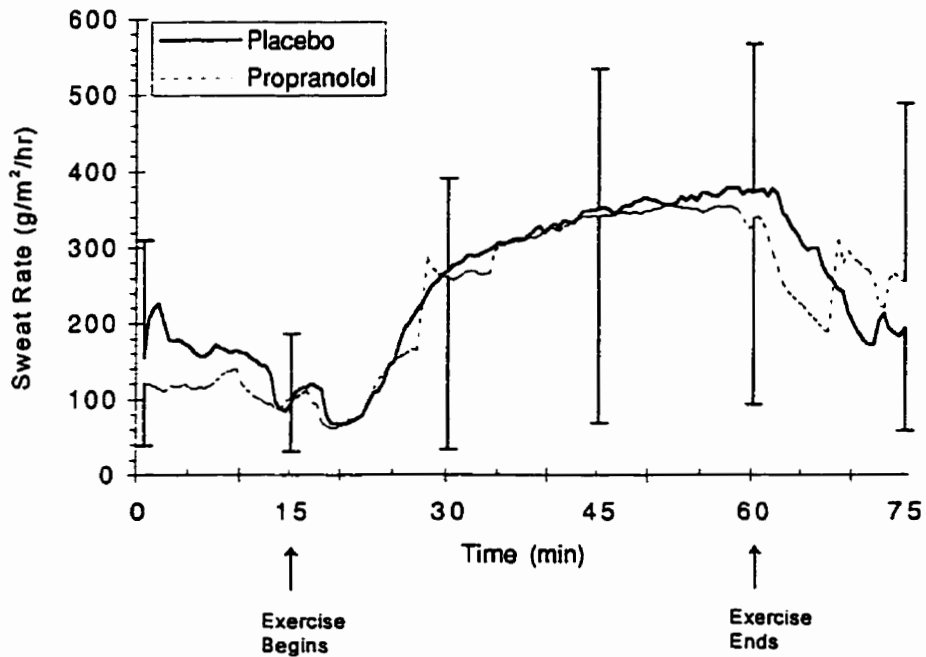


Figure 4-4. Sweat rate (SR) during baseline, exercise and recovery in placebo and propranolol trials (n = 3).

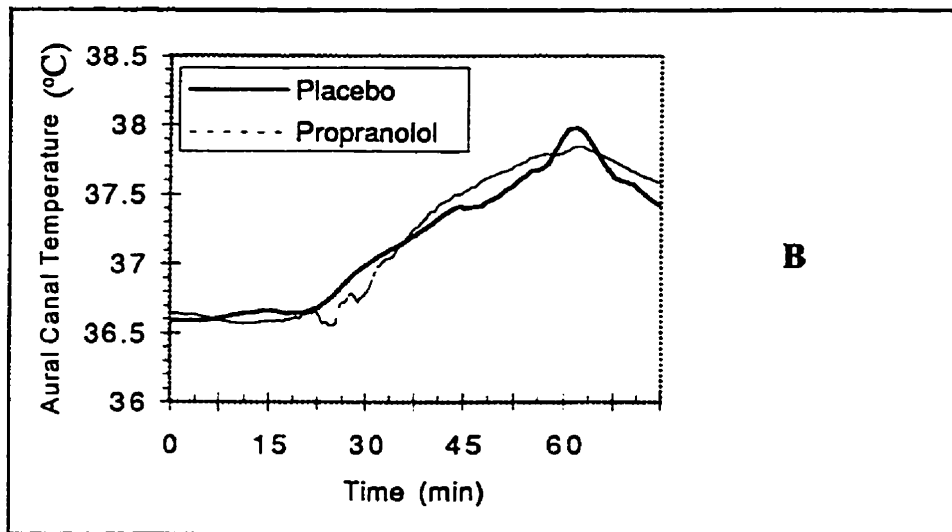
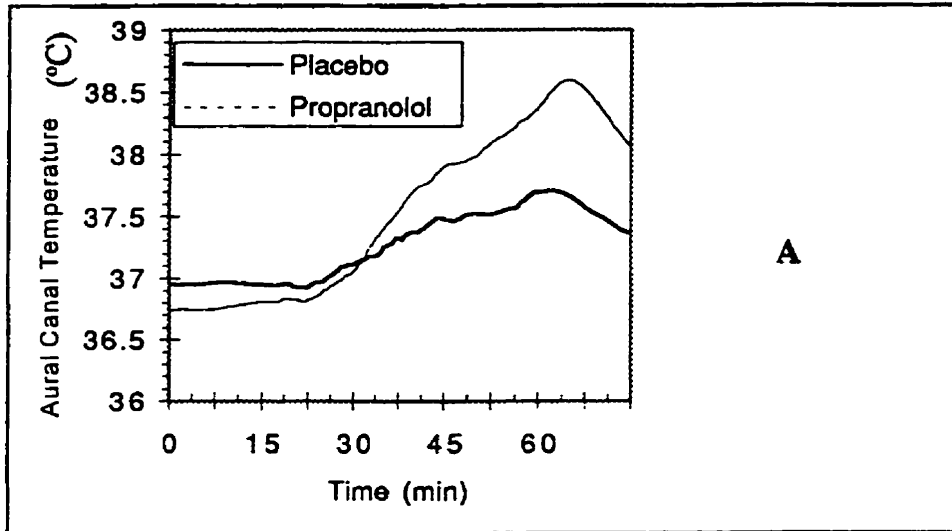


Figure 4-5. Comparison of T_{AC} response to propranolol ingestion in subject #3 (A) and subject #5 (B).

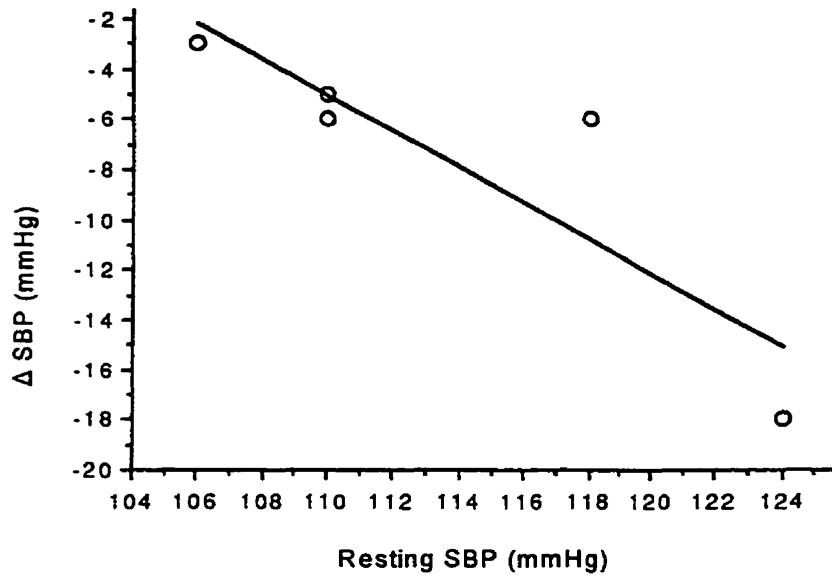


Figure 4-6. Relationship between resting systolic blood pressure (SBP) taken during the initial 12 lead ECG screening and the SBP difference between propranolol and placebo trials ($n = 5$) ($R = 0.876$, $p < 0.05$).

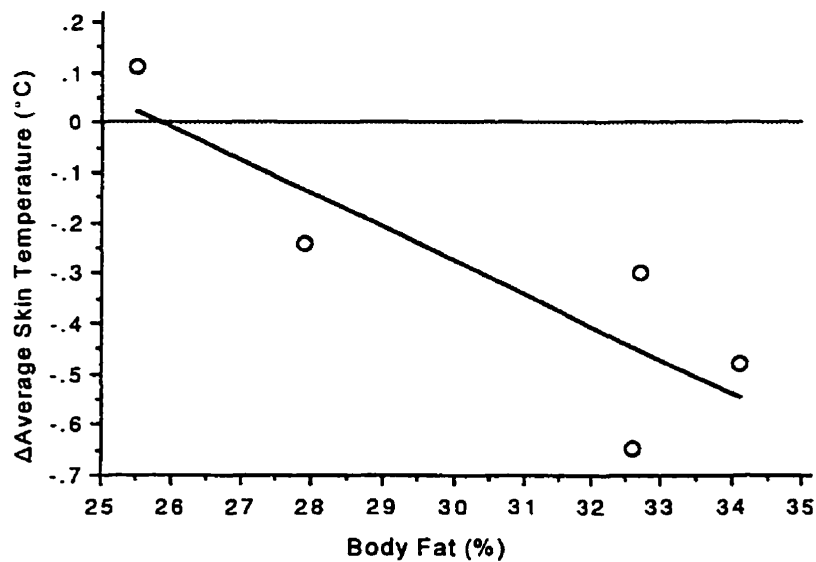


Figure 4-7. Relationship between percentage body fat and the difference in the average skin temperature ($T_{sk,ave}$) between propranolol and placebo trials ($n = 5$). This relationship was not statistically significant.

CHAPTER FIVE: DISCUSSION

Beta blockers are responsible for an entire chain of events (central and peripheral) which can result in enhanced heat storage during exercise and heat stress. As Figure 2-2 demonstrates, these drugs may decrease heart rate and contractility which depresses cardiac output (Q). Decreased Q will cause mean arterial pressure (MAP), a product of Q and total peripheral resistance (TPR), to fall. As a result, the baroreceptor firing rate slows down and the body increases TPR to shift blood centrally. Although this is a normal response to depressions in MAP, it is not necessarily practical in situations of combined exercise and heat stress since centrally shifted blood may decrease T_{SKAVE} and increase T_{CORE} . Beta blockers are also believed to have direct effects on skin blood vessels and sweat glands which limit the body in its ability to provide effective convective and evaporative cooling mechanisms. A decrease in skin blood flow coupled with a depressed sweat rate may also cause an increase in heat storage.

Effect of Beta Blockade on Aural Canal Temperature

The significant change in T_{AC} (ΔT_{AC}) with propranolol during exercise found in this study is in agreement with reports of significantly increased esophageal temperature (T_{ES}) found with non-selective beta blockade (Mack et al., 1986; Pescatello et al., 1987; Pescatello et al., 1990) and supports the original hypothesis. The varying degrees of T_{AC} response between the subjects is of interest, two in particular displaying quite dramatic increases in heat storage with propranolol. The T_{AC} responses of two subjects displayed in Figure 4-5 (A & B) suggests that some individuals may be more prone to significant heat storage with propranolol than others.

The 15 minute recovery period of this study provides for a practical application. Although the difference in the time to peak T_{AC} between the two trials was not significant it bears some discussion. While there was a decrease in T_{AC} during the placebo trial immediately at the end of exercise, peak T_{AC} occurred at two minutes into the recovery period during the propranolol trial. This increase could

become larger when post-menopausal women are subjected to longer or more intense bouts of exercise than those used in this study. Additional research needs to be done addressing the safety of these women after the cessation of exercise in the heat.

Effect of Beta Blockade on Average Skin Temperature

The increased rise in T_{AC} with propranolol can be explained partly by the significant reduction in T_{SKavg} , a finding in agreement with the results of Mack et al. (1986) and one which supports the original hypothesis. However, Gordon et al. (1985) found no change in rectal temperature (T_{RE}) or T_{SKavg} with beta blockade. Pescatello et al. (1987) reasoned that heat transfer from the exercising muscles to the visceral tissue was impaired due to the reduction in splanchnic flow. Therefore T_{RE} may not have been an appropriate representation of T_{CORE} . Although the explanation supplied by Pescatello et al. (1987) for the insignificance of T_{RE} between placebo and drug treatments is a valid one, there may be another explanation. It is plausible that the exercise intervention used by Gordon et al. (1985) may not have been intense enough to invoke changes in T_{RE} . A stable T_{RE} might be expected to be accompanied by a stable T_{SKavg} .

Effect of Beta Blockade on Skin Blood Flow

Another factor controlling T_{CORE} is SKBF. Forearm SKBF was not significantly depressed with propranolol and, therefore, the original hypothesis could not be supported. Other studies have consistently found decreased forearm blood flow with propranolol (McSorley & Warren, 1978; Pescatello et al., 1987; Pescatello et al., 1990). Beta blockers may increase plasma catecholamines and augment alpha vasoconstriction of the skin (Pescatello et al., 1987). Recently, evidence of beta₂ receptors in the skin has generated support although their role during heat stress is not understood (Crandall et al., 1997). Further confirmation of this was supplied as early as 1978 by McSorley & Warren when propranolol (a non-selective beta blocker) significantly reduced SKBF in normotensive and hypertensive men during cycle exercise but metoprolol (a beta₁ selective blocker) did not.

The lack of significance in this study may be attributed to the small subject sample or to the large amounts of artifact which had to be removed from the data set before analysis. Saumet et al. (1988) assure that abrupt increases and decreases in the laser doppler signal are due to motion artifact during exercise rather than to changes in SKBF. Consequently, the forearm may not be the best site for LDF unless the limb can be completely immobilized throughout the exercise task. This particular area was chosen to serve as a comparison to similar investigations in which this site had been successfully used with plethysmography. Despite the lack of significance, forearm SKBF followed a pattern which explains the trend in T_{AC} and T_{SKavg} . A slightly decreased propranolol trial SKBF matched the placebo trial SKBF for approximately 35 minutes (until 20 minutes of exercise) before appearing considerably depressed. This is approximately when the propranolol trial T_{AC} started to rise at a faster rate than the placebo trial T_{AC} . This is in accordance with Patterson et al. (1994) who state that SKBF has been shown to be directly related to changes in T_{CORE} .

Effect of Beta Blockade on Sweat Rate

Results concerning sweat rate (SR) and beta blockade have been controversial. This study witnessed no significant differences in SR between trials during baseline, exercise or recovery. Gordon et al. (1985) found an increase in sweat loss with propranolol and Mack et al. (1986) found a decreased SR and a decreased mean sweat- T_{ES} relationship with beta blockade. It was suggested that these drugs may have depressed the activity of the sweat gland to cholinergic stimulation or decreased the production or release of acetylcholine at the level of the sudomotor nerve resulting in decreased sweat rate (Mack et al., 1986). Although the lack of significance in this study may be attributed to the fact that the data for only three subjects could be used in the analysis, results do not support the original hypothesis. However the findings here may help explain the depressed T_{SKavg} . Under normal conditions of exercise, the increase in T_{SKavg} caused by increased SKBF is balanced by the decrease in T_{SKavg} caused by the cooling effect from increased sweat rate. Consequently there is usually very little

change in T_{SKavg} and sensible heat exchange after sweating has begun (Pandolf et al., 1988). It follows that reductions in SKBF without any appreciable change in sweat rate could be expected to generate decreases in T_{SKave} .

Effect of Beta Blockade on Heart Rate and Blood Pressure

Despite attempts at randomization, the typical depression of heart rate and blood pressure normally serve as indicators of propranolol ingestion. The depression of heart rate in this study with propranolol use is in agreement with other studies (Mack et al., 1986; McSorley & Warren, 1978; Pescatello et al., 1987; Pescatello et al., 1990) and is supportive of the original hypothesis. As Table 4-3 demonstrates, there were varying degrees of heart rate depression among participants, with subjects # 1 and # 3 showing the greatest depression in baseline heart rate with propranolol. This cannot be attributed to the timing between placebo or propranolol ingestion and introduction into the climatic chamber as this was strictly controlled. That there was significant depression of heart rate by propranolol by 30 minutes of exercise is due largely to these two subjects. The average exercise heart rates for subject # 1 and subject # 2 during placebo and propranolol trials respectively (144 bpm and 97 bpm versus 82 bpm and 80 bpm) lends support to the individual variation in beta blocker response. The finding that DBP was not affected by propranolol ingestion and that SBP was not significantly depressed with propranolol during baseline is in agreement with the results of Pescatello et al. (1987), Pescatello et al. (1990) and McSorley & Warren (1978). Although exercise SBP results could not be analysed in this study, these same researches detected significant depression of SBP during exercise. The significant reduction in recovery SBP found here could also not be compared to previous studies as this is the first to include recovery measurements for analysis. Since SBP was not significantly different between trials during baseline, and exercise values of blood pressure were not used, the original hypothesis cannot be supported.

Relationships Between Dependent and Independent Variables

The independent variables used in this study were chosen because they have been implicated in the body's ability to thermoregulate. There was a desire to determine if propranolol worsened the decrease in heat tolerance associated with advancing age, the number of years post menopause, an increase in body fatness and lower cardiovascular fitness levels.

Individual Differences in Response to Propranolol Ingestion

Although "high-responders" to non-selective blockade have been noted in the past (Videmann, Sonck & Janne, 1979), the factors determining such responsiveness are not well documented. One potential factor is the degree of displacement in SBP between trials compared to the resting SBP. It seems possible that those with slightly lower resting SBP may be less likely to respond to propranolol ingestion or at the very least, take much longer to do so. Potential evidence of this is supplied by the fact that SBP was not significantly depressed by propranolol until recovery. Table 4-3 displays comparisons of the five subjects involved in this study and their responses to propranolol. Regression analysis revealed a significant relationship between resting SBP and the difference in baseline SBP between trials ($R = 0.876$, $p < 0.05$) (Figure 4-6). Specifically, those with lower resting SBP tended to encounter less depression in SBP with propranolol. Parati, Mutti, Frattola, Castiglioni, Rienzo & Mancina (1994) determined that baroreceptor sensitivity in hypertensive patients increased significantly after only one month of beta blocker therapy. It is possible that a similar increased sensitivity is present in those with blood pressures at the lower end of the normotensive range. Since SBP is already quite low, increased baroreceptor sensitivity may act to prevent further decreases in MAP. Very slight depressions in SBP may be all that is necessary to invoke valiant attempts at increasing Q. The less dramatic decrease in heart rate with propranolol may be an indication of a system more efficient at preventing decreases in blood pressure. Beta blocker resistance may also be occurring at the level of the beta

receptors in the heart. Further studies identifying beta blocker responsiveness may be useful in determining those individuals who might be at increased risk during exercise and heat stress.

It was noted that two subjects in particular displayed a more dramatic response to propranolol (determined by heart rate and SBP depression). This is important because the entire cardiovascular chain of events described earlier is initially brought about by a decreased heart rate. If heart rate is left virtually unchanged, the resultant decrease in MAP may not be achieved. This can be explained partly by the lack of significant difference in baseline SBP and heart rate values between trials. Despite this recognition of "high-responders" responsiveness was not related to the degree of change in T_{AC} , T_{SKavg} or SKBF between placebo and propranolol trials. Therefore, the fact that there was still a significant rise in T_{AC} with propranolol may be attributed to the direct effect of propranolol on the peripheral blood vessels. Pescatello et al. (1987 & 1990) also dismissed the central effects of beta blockade on thermoregulation. The decrease in heart rate encountered by their male subjects was balanced by an increase in stroke volume sufficient to prevent a decrease in cardiac output. This was attributed to the higher fitness level of their subject sample and they hypothesized that a less fit sample may have been unable to prevent a depression in Q. The concern generated by Pescatello et al. (1987 & 1990) was that less fit individuals may be less able to prevent depressions in Q (a result of decreased heart rate and blood volume) and may therefore experience both the cardiovascular and peripheral effects of beta blockade.

The Relationship of Age and Number of Years Post Menopause and Temperature Regulation

Although past studies suggest that sweat glands and blood vessels are adversely affected by ageing (Anderson & Kenney, 1987; Armstrong & Kenney, 1993; Inoue et al., 1991; Inoue, 1996; Kenney, 1988; Sagawa et al., 1988; Tankersley et al., 1991), increasing age was not related the amount of change in T_{AC} , T_{SKavg} or SKBF between placebo and propranolol trials. Estrogen status also affects thermoregulation (Baker et al., 1994; Carpenter & Nunneley, 1988; Hessemer & Bruck, 1985;

Lieberman et al., 1994; Tankersley et al., 1992). Although estrogen levels were not tested here, the number of years post menopause was not related to any of the dependent variables. This implies that age and the number of years post menopause, do not affect the decrease in heat tolerance experienced with beta blockade.

The Relationship of Body Composition and Aerobic Power and Temperature Regulation

Lower aerobic fitness levels are associated with decreased heat tolerance (Buono et al., 1991; Tankersley et al., 1991) and body composition has also been implicated in the body's ability to thermoregulate (Fox et al., 1989). However, these variables also held no significant relationships with the amount of change in T_{AC} , T_{SKavg} or SKBF between placebo and propranolol trials. Not only was there no significant relationship between peak VO_2 and the chosen dependent variables (Table 4-4), but the subject with the highest peak VO_2 (40.6 ml/kg/min) also had the most dramatic difference in T_{AC} between placebo and propranolol trials (Figure 4-5) experiencing increases in T_{AC} of 1.83 °C and 0.87 °C during her propranolol and placebo trials, respectively. Smith, Hudson, Graitzer & Raven (1988) explained that the enhanced parasympathetic activity found in trained individuals restricts reflex cardiac responses, which accompanied by an attenuated vasoconstrictor response, may result in attenuated MAP control during beta blockade. Therefore, less effective vasoconstriction will not offset a decreased MAP because TPR does not increase sufficiently to do so.

Despite regression analysis failing to reveal any valid predictors of the degree of heat storage experienced with beta blockade during exercise and heat stress, these results should be examined with caution. The sample used in this study was small and, as Table 4-4 demonstrates, some of the R values are deceptively large. Future studies incorporating larger subject samples may reveal different results.

Implications for Exercise Prescription in Older Women

Many older women are not interested in traditional exercise classes (Active Older Adult Course, Red Cross, 1996) and are therefore more likely to exercise outdoors where the environmental temperature and humidity cannot be controlled. The subjects in this study are indicative of this group in their own preferences in physical activities.

Some important implications for program design relate to the fact that not all individuals experience the same degree of heart rate / SBP depression with non-selective beta blockade and that fitness level may not play a role in responsiveness. The combination of potential heart rate depression with beta blockade and heart rate drift in heated environments make using percentages of max heart rate to determine exercise intensity futile. Facilitators should be encouraged to not only continue using the Rating of Perceived Exertion (RPE) charts but to understand why using heart rate values may prove misleading. Participants should also be periodically asked if they are feeling faint to ensure they are not experiencing any sudden decreases in blood pressure. It should also be recognized that although RPE is useful, some participants may not be consciously aware of any problems associated with heat storage. None of the women in this study noticed any differences in the level of difficulty between exercising while drug-induced and exercising drug free despite the finding of greater heat storage with Propranolol. Facilitators should therefore be familiar with the side effects of beta blockers (lightheadedness, lethargy) and check with those on these medications before the activity session has begun. Careful attention should also be paid to the recovery period as T_{AC} continued to rise for an additional two minutes after the cessation of exercise and it should be considered that exercise cessation does not necessarily mean an instantaneous fall in T_{CORE} . Therefore, those on beta blocker medication should continue to monitor how they are feeling after the end of exercise.

Elements beside beta blockers, such as decreased skin blood flow and sweating rates with advancing age, may place older women at risk in the heat and certain medications such as hormonal

replacement therapy may provide some relief. The length of time the individual has been on the medication should also be taken under consideration. Since Parati et al. (1994) determined that baroreceptor sensitivity in hypertensive patients increases significantly after only one month of beta blocker therapy it is therefore possible that those new to beta blocker therapy may be at greater risk during exercise and heat stress.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

This is the first investigation of the effects of beta-adrenergic blockade on post-menopausal women during exercise and heat stress. Significant increases in T_{AC} and decreases in T_{SKavg} and heart rate are consistent with previous findings in men and support the original hypotheses. Although results regarding SKBF, SR and blood pressure did not support the hypotheses, past research notes the effects of ageing on thermoregulation. A combination of potential decreases in SKBF and sweat efficiency with advancing age, the effects of estrogen depression associated with post-menopause and the common use of beta blocking drugs may place older women at increased risk during combined exercise and heat stress. These factors should be given serious thought when designing exercise programs for older women.

Although the effects of short term use of beta blockade on thermoregulation have become more evident over the years, more research in this area is warranted. Since an increase in baroreceptor sensitivity is obtained after one month of propranolol use (Parati et al., 1994), longitudinal studies focussing on older women commencing beta blocker therapy should shed light on the chronic effects these drugs have on thermoregulation during exercise in the heat. Since medication of this type is often taken for the rest of the individual's life, it is necessary to study the effects of beta blockade during exercise and heat stress into the seventh and eighth decades of life. Additionally, measurements continued into a period of recovery will indicate whether longer or more intense bouts of exercise than those used in this study result in longer times to peak core temperature.

Since responsiveness to beta blockers has been noted in previous studies (Videmann et al., 1979) further research may help identify other factors associated with this phenomenon and those who may be at increased risk during exercise in the heat. Regression analysis revealed no relationships between dependent and independent variables here, however, due to the small number of women involved future investigations incorporating larger subject samples are warranted.

Estrogen has been implicated in thermoregulation (Baker et al., 1994; Carpenter & Nunneley, 1988; Hessemer & Bruck, 1985; Lieberman et al., 1994; Tankersley et al., 1992), therefore, studies combining subjects on hormonal replacement therapy with those who are not may indicate whether or not this common practice proves beneficial for older women on beta blockers. Finally, investigations incorporating the effects of other common prescription medications on heat tolerance may prove useful. Due to the growing trend of exercise prescription for older adults further research encompassing exercise and thermoregulation will help ensure the safety of these individuals.

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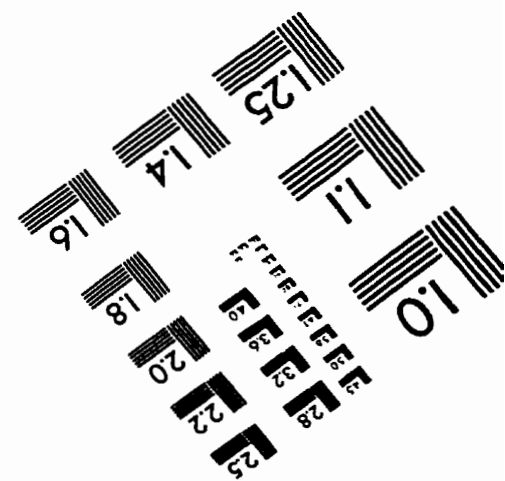
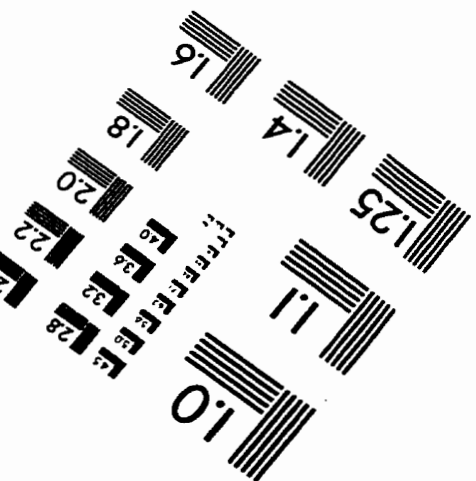
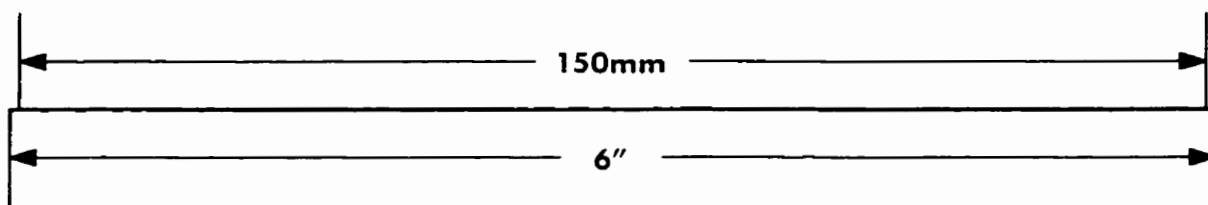
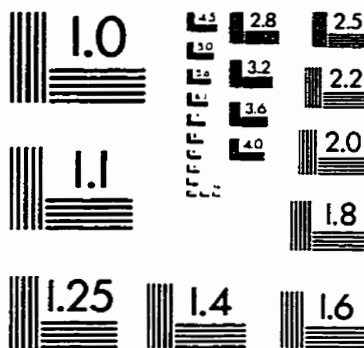
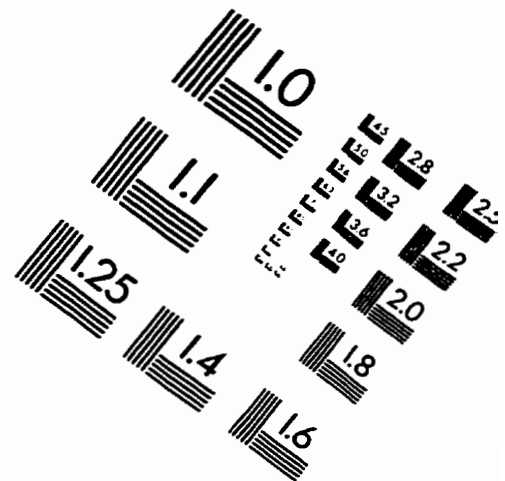
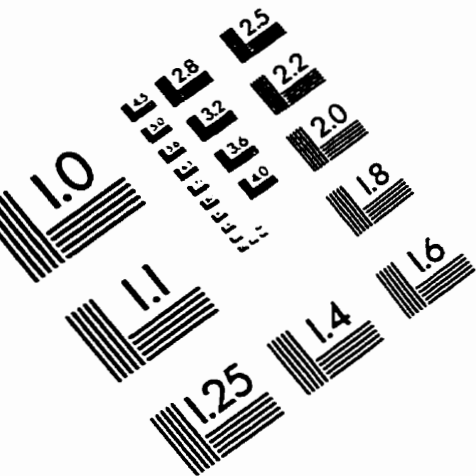
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IMAGE EVALUATION TEST TARGET (QA-3)



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