

Cooling via one hand improves physical performance in heat-sensitive individuals with Multiple Sclerosis: a preliminary study.

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Abstract

Background. Many individuals afflicted with multiple sclerosis (MS), experience a transient worsening of symptoms when body temperature increases due to ambient conditions or physical activity. Resulting symptom exacerbations can limit performance. We hypothesized that extraction of heat from the body through the subcutaneous retia venosa that underlie the palmar surfaces of the hands would reduce exercise-related heat stress and thereby increase the physical performance capacity of heat-sensitive individuals with MS.

Methods. Ten ambulatory MS patients completed one or more randomized paired trials of walking on a treadmill in a temperate environment with and without cooling. Stop criteria were symptom exacerbation and subjective fatigue. The cooling treatment entailed inserting one hand into a rigid chamber through an elastic sleeve that formed an airtight seal around the wrist. A small vacuum pump created a -40 mm Hg subatmospheric pressure environment inside the chamber where the palmar surface of the hand rested on a metal surface maintained at 18-22°C. During the treatment trials, the device was suspended from above the treadmill on a bungee cord so the subjects could comfortably keep a hand in the device without having to bear its weight while walking on the treadmill.

Results. When the trials were grouped by treatment only, cooling treatment increased exercise durations by 33% (43.6 ± 17.1 min with treatment vs. 32.8 ± 10.9 min. without treatment, mean \pm SD, $p < 5.0 \cdot 10^{-6}$, paired T-test, $n = 26$). When the average values were calculated for the subjects who performed multiple trials before the treatment group results were compared, cooling treatment increased exercise duration by 35% (42.8 ± 16.4 min with treatment vs. 31.7 ± 9.8 min. without treatment, mean \pm SD, $p < 0.003$, paired T-test, $n = 10$).

Conclusion. These preliminary results suggest that utilization of the heat transfer capacity of the non-hairy skin surfaces can enable temperature-sensitive individuals with MS to extend participation in day-to-day physical activities despite thermally stressful conditions. However, systematic longitudinal studies in larger cohorts of MS patients with specific deficits and levels of disability conducted under a variety of test conditions are needed to confirm these preliminary findings.

Background

For individuals with multiple sclerosis (MS) symptom exacerbation can be a limiting factor for physical activity. Up to 80% of individuals with MS report symptom exacerbation associated with heat stress resulting from exercise, exposure to elevated environmental temperatures, or both [1-5]. Exercise-induced MS symptom exacerbations are the result of an accumulation metabolic heat generated by the working skeletal muscles [6-8]. To mitigate the worsening of symptoms during exercise, heat production must be reduced or heat loss increased. Heat production is proportional to work output and, thus, can only be reduced by decreasing the level of physical activity. Currently available means for increasing heat loss are either: 1) selecting an optimal (i.e., cool) environment or 2) creating a cool microclimate by wearing cooling garments. A means to directly facilitate heat removal from the body core could forestall the onset of symptom exacerbation and enable heat-sensitive individuals to increase their endurance capacity during physical activity or exposure to elevated environmental temperatures.

Specialized subcutaneous vascular structures [arteriovenous anastomoses (AVAs) and associated retia venosa] underlie the non-hairy skin surfaces of the human body (the palms of the hands, the soles of the feet, the ears, and face) [9]. These unique vascular structures distribute a large volume of blood over a two dimensional plane just beneath the skin surface. During extreme heat-stress blood flow through the subcutaneous AVAs can be as high as 8 l/min (60% of the cardiac output) [10]. Blood flow through these specialized vascular structures provides a means for heat accumulated within the body to be transferred efficiently to the external environment [11]. The venous blood returning from these vascular beds can have a significant effect on the temperature of the body core, and especially on organs and active muscles that are receiving high percentages of the cardiac output [12-18].

We have developed a portable means for optimizing heat exchange through the retia venosa underlying the non-hairy skin surfaces of the hands and feet [19-21]. A hand or foot is enclosed in an air tight chamber and a pressure differential is used to expand the rete venosum of the enclosed appendage and thereby draw an increased blood volume into it. Through the combined local application of low level subatmospheric pressure and an appropriate thermal load, it is possible to transfer a substantial amount of heat into or

out of the circulating blood and, thereby, directly manipulate core temperature using only a single hand [19-22]. This heat extraction method decreased the rates of core temperature rise and improved the physical performances of fit and active individuals during aerobic exercise in a hot environment [20, 22]. We questioned whether use of this technique would provide a similar benefit to heat-sensitive individuals with MS.

Methods

Subjects: Six male and six female ambulatory individuals with MS volunteered to participate in the study. All subjects reported heat-related MS symptom exacerbations and participated in regular exercise programs. The sex, age, MS classification and primary symptoms of each subject are tabulated in Table 1. Informed consent was obtained from each subject using an instrument approved by the Stanford University Institutional Review Board. Each subject was assigned an alphanumeric identifier which was used thereafter in accordance with Health Insurance Portability and Accountability Act guidelines.

Facilities and Monitoring equipment: Trials were conducted on a stationary treadmill (Nordic Track model 9800). The ambient conditions were $23.0 \pm 1.0^{\circ}\text{C}$, 10-25% relative humidity. Heart rate monitors/data loggers (model S810, Polar Electro Oy, Kempele, Finland) collected heart rate data at 5 second intervals. Hand-written data logs noted subject identifier, date, treatment, exercise duration, and miscellaneous comments. Exercise durations were timed using a commercially available stop watch (four-channel alarm timer, VWR).

Heat Extraction Device: The heat extraction device (AVAcore Technologies, Ann Arbor, MI) consisted of a rigid chamber into which one hand was inserted through an elastic sleeve that formed a flexible airtight seal around the wrist. The rigid chamber was connected to a pressure sensor and a vacuum pump. The vacuum pump created a slight subatmospheric pressure environment inside the chamber (-40 mm Hg) where the palm rested on a curved metal surface that was maintained at 18-22°C by temperature-controlled water circulated beneath the metal surface. The device was suspended from the ceiling by an elastic cord during the exercises to reduce the imposition of wearing the device on gait, stride, and posture while walking.

Protocol: Each subject was equipped with a heart rate monitor prior to all trials. The stop criterion for all exercise trials was symptom exacerbation or subjective fatigue. Baseline assessments of individual physical performance capacities were conducted on day 1. For this assessment the subject began walking on a level treadmill at 0.8 Km/hr (0.5 mi/hr). At three minute intervals the speed or slope of the treadmill was alternately increased. The speed was increased by 0.8 Km/hr increments up to a maximum speed of 5.6 Km/hr (3.5 mi/hr). The slope of the treadmill was increased by 1% increments. Once the treadmill speed reached 5.6 Km/hr, only the slope was incrementally increased. For the subsequent experimental trials the speeds and slopes of the treadmill were adjusted to approximate 65% of the maximum work load achieved by the individual subject during his or her baseline trial. The workload for each subject was kept constant for the pair of experimental trials.

An experimental trial consisted of the subject walking on the treadmill at a predetermined speed and slope until a stop criterion was reached. Experimental trials were initiated not less than two days after the baseline assessment trial and separated by a minimum of two days and a maximum of seven days. The subjects returned to the laboratory at the same time of day for all of their trials. All subjects performed a minimum of two experimental trials, one without using the heat extraction device and one using the device. The daily experimental routine consisted of a fifteen min rest in a sitting position, a 3 min warm-up walk at 1.6 Km/min and 0% slope, the experimental trial, and 30 min of seated recovery. On days when cooling treatments were administered, the heat extraction device was donned prior to the onset of treadmill activity. The order of the treatments was randomized. Water was available to the subjects *ad libitum* throughout the trials.

Statistical Analysis: Heart rates were plotted for each trial and exercise durations tabulated on a spreadsheet (Microsoft Office Excel). The exercise duration data were analyzed in two ways: 1) If subjects completed more than one set of paired trials, mean exercise durations were calculated for each individual's control and treatment trials. The individual subjects' mean exercise duration data were then grouped according to treatment. Group mean and standard deviation were calculated for each treatment and the data were compared with a paired t-test. The proportional effects of treatment were

determined by dividing exercise duration with heat extraction by exercise duration without heat extraction. 2) All sets of paired trial data were grouped according to treatment and the data plotted as exercise duration with treatment vs. exercise duration without treatment. The plotted data were subjected to a curve fitting analysis using the data analysis tools provided with Microsoft Office Excel. Mean and standard deviations were calculated for treatment grouped data and the data were compared with a paired t-test.

Results

A total of 88 experimental trials were conducted on the twelve subjects. Two subjects experienced relapses and dropped out of the study without completing a set of paired trials. Twenty six data sets that met the criteria for paired trials (identical work loads and a maximum of seven days separating the trials) were collected from the remaining ten subjects. Cooling treatment increased performance (Table 2). When the individual subject's mean data were analyzed according to subject and treatment, treatment extended exercise duration by an average of 35% (42.8 ± 16.4 with cooling compared to 31.7 ± 9.8 minutes without cooling, mean \pm standard deviation, $n=10$, $p<0.003$, paired t-test) and ranged from 8% to 65%.

When the exercise duration data were analyzed according treatment only ($n=26$), mean exercise duration with treatment was 43.6 ± 17.09 min (mean \pm SD) compared to 32.8 ± 10.9 without treatment: a mean increase of 33% ($p< 5.0 \cdot 10^{-6}$, two tailed paired t-test). The magnitude of the treatment effect was correlated with exercise duration during the control trials (Figure 1). Ninety percent of the variance in the improvements with the treatment could be accounted for by an exponential function fitted to the data ($y = 12.505e^{0.0356x}$ with y and x being exercise duration with treatment and without treatment, respectively).

There were no discernable patterns in heart rates (Figure 2). Cardiac drift - a rise in heart rate during sustained fixed load exercise - was observed in all trials. Initial heart rate, final heart rate, and rate of cardiac drift (change in heart rate/time) varied among the subjects and trials. The rate of cardiac drift was proportional to neither work load nor exercise duration time. Treatment did not affect the cardiac drift in a consistent manner:

in some cases treatment increased cardiac drift; in others, treatment decreased cardiac drift; while, in others, treatment had no effect heart rate patterns.

Anecdotally, most subjects reported feeling better during the cooling trials. Several subjects reported that instead of experiencing the usual progressive fatigue when exercising, their symptoms occurred in waves when they used the heat extraction device. Another subject reported experiencing an unusual set of symptoms when treated. Instead of feeling “cloudy” during exercise, he felt a tingling in his legs.

Discussion

The outcome measure in this study was physical performance rather than changes in core temperatures. The effects of temperature on individuals with MS are well known: increases in temperatures often exacerbate symptoms while decreases in temperatures can improve them [4, 23-25]. However, the magnitude of thermal stimulus necessary to elicit a symptom exacerbation in MS patients can be minor and may be insufficient to be noted as a change in a measured deep body temperature [26]. Substantial improvements in fatigue, muscle strength and standing balance were observed when individuals with MS were actively cooled using cooling garments, but there was not an associated effect of lowering tympanic temperatures [27]. Since the effects of cooling have been demonstrated without an associated affect on core temperatures and placement of a core temperature probe can be stressful and unpleasant for the subjects, core temperatures were not measured in this study. The cause of physical performance improvements could be multi-factorial and thus, without a direct measure of core temperature, we can only speculate that that the cooling treatment used in these studies provided a cooling benefit which resulted in the performance improvement. Given the multitude of published reports on the effects of thermal manipulation of the hands or feet on core temperatures and performance [12-22] and on the effects of thermal manipulations on performance [8, 26-28] and symptom exacerbation [23-25] in individuals with MS, this is a reasonable inference.

The effects of manipulating the internal thermal condition of MS patients by delivering a thermal load to a single appendage have been noted previously [23, 24]. In 1950 Guthrie observed that MS patients became extremely weak while sitting in a hot water bath. A similar response could be elicited in those subjects by simply immersing a

single arm or leg in hot water. An arterial tourniquet during arm immersion suppressed the symptom exacerbations. At the time it was theorized that the underlying mechanism for the heat response of the MS patients to limb immersion was due to a humoral factor, a reflex vasomotor response, or to a change in cerebral blood flow. An alternative explanation put forth at that time and discounted was that adequate amounts of heat were being delivered through one hand to increase core temperature thereby inducing symptom exacerbation.

MS is a disease of the central nervous system (CNS). Presumably, the heightened temperature sensitivity of MS patients is CNS-mediated. Increases in CNS temperature, rather than body temperature per se, cause heat related symptom exacerbations [26]. The brain and spinal cord are metabolically stable tissues that generate metabolic heat at a constant rate [29]. Heat is removed from CNS tissues through the vascular system. Thus, the temperature of the CNS is determined primarily by the temperature of the arterial blood [29, 30]. If the temperature of the arterial blood is elevated, CNS temperatures will rise. Substantial heat is produced by working skeletal muscles during physical activity. Heat generated by skeletal muscles is removed from the muscle by the circulation. The warmed venous blood from active skeletal muscles is mixed with other venous return blood as it passes through the heart and pulmonary circulation. Any thermal manipulation that delivers a cool thermal load to the venous return blood will counteract the effects of the heat produced by active skeletal muscles. By accessing the circulating blood flowing through the retia venosa underlying the non-hairy skin surfaces it is possible to directly cool large volumes of venous blood.

The results reported here agree with those of previous studies that examined the effects of cooling on ambulatory performance in heat-sensitive individuals with MS patients; cooling can improve performance [8, 28]. In the previously reported studies the subjects were cooled for 30 min prior to fixed duration exercise bouts followed by evaluation[8] or for 60 min between evaluations [28]. Evaluation of physical performance was time and number of steps required to complete a 25 foot walk. In those studies the thermal loads were delivered to the general skin surface via a circulating water garment[28] or by cold water immersion [8]. Applying a cool load to the general skin surface directly affects the thermal inertia of the skin and underlying tissues. However,

application of a thermal load to the general skin surface has little direct effect on the metabolically active core organs because the hairy skin surfaces are poorly perfused and therefore insulate the body core from the external thermal environment [31, 32].

Applying cooling to the general body surface takes advantage of the thermal inertia of poorly perfused superficial and peripheral tissues, however, to store a cold load [8]. This cold load in the periphery then passively absorbs heat conducted into it by the blood flow and is the reason that precooling can improve endurance [33]. Conversely, with heat exchange involving the retia venosa, the thermal load is applied directly to the blood flowing through the palm during exercise. Cooling a volume of circulating blood directly affects the highly perfused core organs.

Precooling has been reported to result in lower heart rates during subsequent fixed load exercise in MS subjects [8]. The difference in effect of cooling treatment on heart rate between the previous report and the results reported here is likely methodological. Precooling the peripheral tissues likely induced a vasoconstriction response that reduced blood flow to the skin and peripheral tissues. Peripheral vasoconstriction increases peripheral resistance resulting in a rise of arterial pressure and a subsequent baroreceptor response decreasing heart rate.

The ability to effectively remove of heat from the body could substantially improve the daily lives of heat sensitive individuals with MS. Critical body surface regions for direct heat exchange are the non-hairy regions that contain the subcutaneous arteriovenous anastomoses and retia venosa. Heat transfer devices incorporated into gloves or shoes could augment the use, or be used in lieu, of currently available cooling garments. The heat transfer devices used in this study used a pressure differential to maximize heat exchange. It has been demonstrated that, under certain conditions, substantial heat can be extracted from the body through the non-hairy skin surfaces without the application of a pressure differential [12-17]. The application of a cool load alone to the non-hairy skin surfaces may provide a benefit to heat sensitive individuals with MS under some heat-stress conditions.

Conclusion

The results from this preliminary study demonstrate that, under a set of specific test conditions and in a small group of subjects who were selected in part because they

engaged in regular exercise, utilization of the heat transfer capacity of the non-hairy skin surfaces can enable temperature-sensitive individuals with MS to extend participation in physical activities. Systematic longitudinal studies in larger cohorts of MS patients with specific deficits and levels of disability conducted under a variety of test conditions in independent research facilities are needed to confirm these preliminary findings. If these initial findings are replicated in future studies, the development of small wearable heat transfer equipment in the form of gloves or footwear could provide a benefit individuals with MS.

Competing interests

Patents have been issued for the technology disclosed in this manuscript [D. Grahn and H.C. Heller (Inventors); Stanford University (Assignee)], and Stanford University has entered into a licensing agreement with AVAcure Technologies, Inc., for the commercialization of the technology. Included in the license is a royalty agreement that grants Stanford University a percentage of the net sales of the technology, which will be shared by the University and the inventors. D. Grahn and H.C. Heller are founders of AVAcure Technologies but receive no ongoing compensation from the company. AVAcure Technologies provided no financial support for this research.

To eliminate the possibility of this potential conflict of interest influencing the outcome of the research Stanford University requires that Grahn and Heller have no ongoing participation in the recruitment of subjects, the conduct of the experimental trials, and/or the analysis of the data.

Authors' Contributions

DAG, JvLSM, and HCH made substantial intellectual contributions to this study. DAG, JvLSM, and HCH were involved in the conception and design of the study, the interpretation of the data, and the drafting and revising of the manuscript. JvLSM was also involved in recruitment of the subjects, and data acquisition and analysis. All authors have read and approved the final manuscript.

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Figure Legends

Figure 1. The effect of hand cooling on exercise duration: a comparison of twenty-six paired treatment trials. The effect of treatment (cooling) was affected by exercise duration during the control condition. The longer the duration of exercise in the control condition, the greater the cooling treatment effect. An exponential function ($y = 12.505e^{0.0356x}$) accounted for 90% of the variance in the data. The solid line was generated by the exponential function; the dashed line represents unity. Inset: mean \pm SD exercise duration with treatment and without treatment (43.6 ± 17.09 min. with treatment vs. 32.8 ± 10.9 min. without treatment ($p < 5.0 \cdot 10^{-6}$, two tailed paired t-test, $n=26$)).

Figure 2. The effect of cooling on heart rate during exercise. Examples of heart rates during paired control and experimental trials from 5 subjects. Open symbols control, closed symbols cooling. While treatment (cooling) had little effect on heart rate, there were substantial differences between individual subject heart rates. This inter subject variability in heart rate was due in part to differences in work loads among subjects.

Table 1: Gender, age, and diagnosis of individual subjects.

Subject	Gender	Age	Type	Primary symptoms
1	M	45	RR	Leg muscle weakness, cognitive difficulties
2	M	63	RR	Spasticity, cognitive difficulties
3	M	42	RR	Fatigue, balance, cognitive difficulties
4	F	53	RR	Fatigue, balance, spasticity
5	M	46	RR	Leg motor control, balance
6	M	55	SP	Limb weakness
7	F	55	RR	Fatigue, postural muscle weakness
8	F	55	SP	Leg motor control
9	M	53	RR	Ataxic gait, cognitive difficulties
10	F	56	RR	Leg muscle weakness, spasticity, fatigue
11	F	42	RR	Vertigo ^a
12	F	45	RR	Limb weakness ^a

RR-Relapsing Remitting, SP- Secondary Progressive.

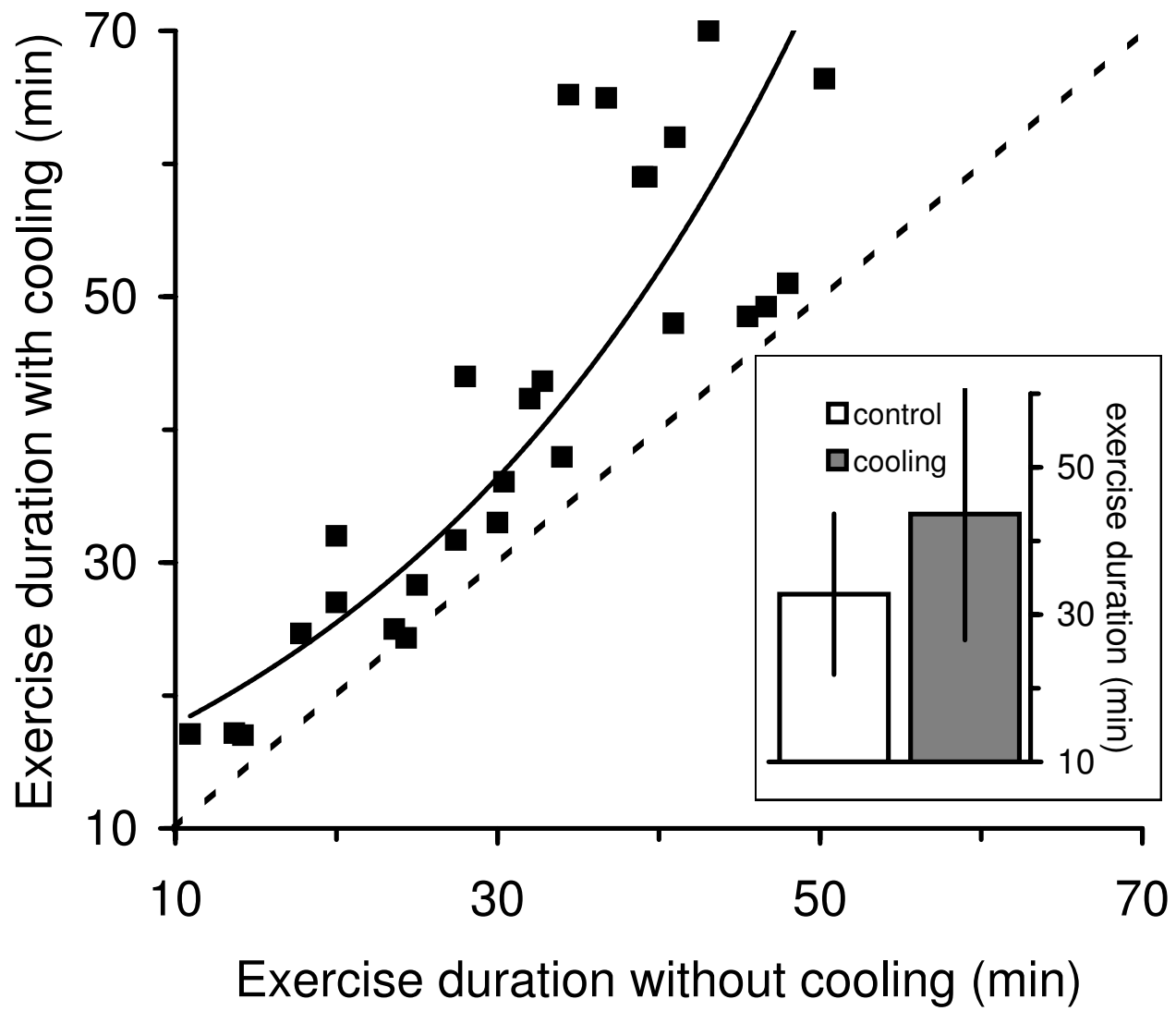
^a subject withdrew from study due to self-reported relapse.

Table 2. Treadmill speed and slope, number of paired trials, mean trial times and effect ratio (exercise duration with cooling/exercise duration without cooling): individual subjects and grouped data

Subject #	Speed ^a (Km/h)	Slope ^a (%)	# paired trials	Exercise duration (min)		Cooling effect (ratio)
				Control	Cooling	
1	4.8	5 - 6	3	17.2	22.9	1.34
2	0.8	0	1	20.0	32.0	1.60
3	4.0	5 - 6	3	20.7	22.1	1.07
4	1.3	0	1	25.0	28.3	1.13
5	3.2 - 4.8	6	4	36.4	44.8	1.23
6	4.8	7 - 8.5	3	37.4	49.8	1.33
7	4.0	6 - 7	5	38.4	51.6	1.34
8	2.4	0	2	39.8	43.2	1.09
9	3.2	0	2	39.9	67.5	1.69
10	3.2	5.5 - 6	2	42.3	65.8	1.55
Group data ^b						
Mean ± Standard Deviation				31.7 ± 9.8	42.8 ± 16.4	1.35 ± 0.22

^a When necessary, slopes and speeds of the treadmill were adjusted between sets of paired trials.

^b P <0.01, paired t-test



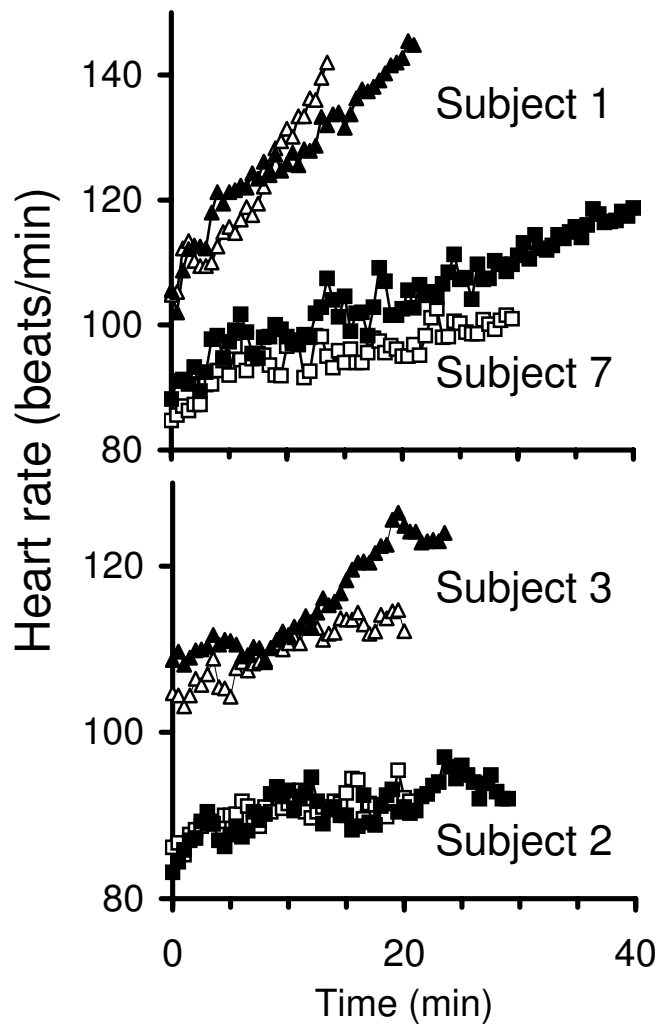


Figure 2