Localized β-adrenergic receptor blockade does not affect sweating during exercise

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Buono MJ, Tabor B, White A. Localized β-adrenergic receptor blockade does not affect sweating during exercise. Am J Physiol Regul Integr Comp Physiol 300: R1148–R1151, 2011. First published February 16, 2011; doi:10.1152/ajpregu.00228.2010.—The purpose of the current study was to determine the effect of a locally administered nonselective β-adrenergic antagonist on sweat gland function during exercise. Systemically administered propranolol has been reported to increase, decrease, or not alter sweat production during exercise. To eliminate the confounding systemic effects associated with orally administered propranolol, we used iontophoresis to deliver it to the eccrine sweat glands within a localized area on one forearm prior to exercise. This allowed for determination of the direct effect of β-adrenergic receptor blockade on sweating during exercise. Subjects (n = 14) reported to the laboratory (23 ± 1°C, 35 ± 3% relative humidity) after having refrained from exercise for ≥12 h. Propranolol (1% solution) was administered to a 5-cm2 area of the flexor surface of one forearm via iontophoresis (1.5 mA) for 5 min. A saline solution was administered to the opposing arm via iontophoresis. Each subject then exercised on a motor-driven treadmill at 75% of their age-predicted maximal heart rate for 20 min, while sweat rate was measured simultaneously in both forearms. Immediately after cessation of exercise, the number of active sweat glands was measured by application of iodine-impregnated paper to each forearm. The sweat rate for the control and propranolol-treated forearm was 0.62 ± 41 and 0.60 ± 0.44 (SD) mg·cm−2·min−1, respectively (P = 0.86). The density of active sweat glands for the control and propranolol-treated forearm was 130 ± 6 and 134 ± 5 (SD) glands/cm2, respectively, (P = 0.33). End-exercise skin temperature was 32.9 ± 0.2 and 33.1 ± 0.3°C for the control and propranolol-treated forearm, respectively (P = 0.51). Results of the current study show that when propranolol is administered locally, thus eliminating the potential confounding systemic effects of the drug, it does not directly affect sweating during the initial stages of high-intensity exercise in young, healthy subjects.

propranolol; cholinergic; adrenergic; eccrine sweat gland

HEAT DISSIPATION IS CRITICAL for human survival in hot environments and particularly during high-intensity exercise. Thermoregulatory sweating in humans is produced by the ~2–3 × 106 eccrine glands located in the skin. Neural afferents provide information concerning the thermal status of the body core and shell (i.e., skin) to the preoptic anterior hypothalamus. After integration of the signals, thermoregulatory sweating occurs when the mean body temperature exceeds the sweating threshold, usually 0.2–0.5°C above thermoneutrality. The sudomotor signal descends through the brain stem and spinal cord, and postganglionic, nonmyelinated class C fibers ultimately innervate the eccrine glands (21, 25, 26). It is well known that human sweat glands are innervated by the cholinergic and adrenergic systems (19, 21–24, 28). However, it is generally believed that sweating during exercise is predominantly controlled via the cholinergic system (24–26). For example, Sato and Sato (22) examined the in vitro sweat response of eccrine sweat glands to cholinergic and adrenergic agonists. They reported that the relative effects on sweat production are 4:2:1 for cholinergic, β-adrenergic, and α-adrenergic receptor stimulation, respectively. Conversely, it has recently been reported that in vivo β-adrenergic stimulation alone is not sufficient to elicit sweating in exercising humans (3). Thus the exact role of the β-adrenergic system during sweating is unknown (16, 26).

One of the more common research designs used to examine the potential role of adrenergic innervation in sudomotor function is measurement of sweating during exercise before and following β-adrenergic receptor blockade by propranolol (9, 10, 13, 17, 18, 31). However, a review of the literature reveals that the effect of β-blockade on sweating during exercise is controversial (17). For example, Wilcox et al. (31) found that sweating during exercise was increased 66% following the oral administration of 80 mg of propranolol compared with the control trial. Conversely, Pescatello et al. (17) reported that the slope of the chest sweat rate- esophageal temperature relationship was significantly reduced following ingestion of 80 mg of propranolol. In fact, oral propranolol administration has been shown to increase (9, 10, 31), decrease (13), or have no effect (17) on whole body sweat rate during exercise. A likely cause for such divergent results is the fact that oral administration of propranolol is known to have a variety of systemic effects. Cardiovascular perturbations include reductions in heart rate (18, 31), blood pressure (9, 18, 31), skin blood flow (9, 17, 18), cardiac output (9, 17), and skeletal muscle blood flow (1). Furthermore, oral administration of propranolol has been shown to reduce skin temperature (9, 13) and increase core temperature (13, 18) during exercise. In addition, β-blockade has been shown to significantly affect skeletal muscle metabolism during exercise (1, 5, 29). Thus oral propranolol administration may be affecting thermal and various nonthermal (e.g., baroreceptor, metaboreceptor, mechanoreceptor) modulators of sweating during exercise (25, 26), thus confounding the results.

Several recent studies (6, 27) have shown that propranolol can be successfully delivered through the skin to the eccrine sweat glands via iontophoresis, using direct currents as small as 50 μA for 10 min. For example, Stagni et al. (27) used microdialysis probes inserted 2 mm into the dermis of the forearm of healthy subjects to successfully quantify the pharmacokinetics of iontophoretically delivered propranolol using a constant current of 0.2 mA. They found that, following the onset of iontophoresis, propranolol started to rapidly appear in the dialysate and continued to appear for ≥1 h following cessation of iontophoresis.
In light of the above-described controversy, the purpose of the current study was to determine the effect of a locally administered nonselective β-adrenergic antagonist on sweat gland function during exercise. It was hypothesized that when the confounding systemic effects associated with oral propranolol were eliminated, the local administration of a nonselective, β-adrenergic antagonist would have no effect on sweat gland function during exercise.

METHODS

Fourteen healthy volunteers (8 men and 6 women) participated in this study; their characteristics (means ± SD) are as follows: 25 ± 2 yr old, 171.8 ± 15.8 cm stature, and 67.2 ± 9.4 kg body wt. The study was approved by the San Diego State University Institutional Review Board. Signed informed consent was obtained from each subject prior to testing. In addition, female subjects took a urine pregnancy test and propranolol were eliminated, the local administration of a nonselective, β-adrenergic antagonist would have no effect on sweat gland function during exercise.

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Subjects reported to the laboratory after having refrained from exercise for ≥12 h. The ambient air temperature and relative humidity in the laboratory were 23 ± 1°C and 35 ± 3% during all data collection. A 1% propranolol solution in saline was prepared by one of the investigators within 10 min of the start of each exercise bout and administered to a 5-cm² area of the flexor surface of one forearm via iontophoresis (1.5 mA) for 5 min. A saline solution was administered to the opposing arm via iontophoresis. The arm that received the propranolol treatment was randomly assigned. It has been shown that iontophoresis in and of itself does not increase axon reflex or local sweating in the human forearm (11).

The subject then warmed up by running on a motor-driven treadmill at 75% of his/her age-predicted maximal heart rate (147 ± 6 beats/min) for 5 min. It has been shown (12) that exercise at this intensity results in a 10-fold increase in systemic sympathetic activation compared with rest, as measured by norepinephrine spill-over. Heart rate was measured during exercise using a Polar heart rate monitor. After the 5-min warm-up period, the forearms were blotted dry, and a Macroduct (Wescor, Logan, UT) was placed on each forearm to simultaneously collect sweat from both iontophoresis sites. Macroduct sweat collectors have a shallow conical surface design, which provides a low-dead-space (~3 μl) contact with the sweating skin surface. The sweat is collected via capillary action in a coiled tube, preventing evaporation (30). In our laboratory, simultaneously measured sweat rates on both forearms during exercise using Macroducts are highly correlated (r = 0.95). Since sweat rate does not immediately increase at the start of exercise, Macroducts were applied after the 5-min warm-up period to allow the subjects to start sweating prior to the initiation of data collection. Each Macroduct was securely attached to the skin surface with Velcro straps, which prevented sample leakage and contamination. Subjects continued exercising at the same intensity for another 15 min, during which sweat was collected. Immediately after cessation of exercise, the skin temperature of both forearms was measured using an infrared technique (4). Core body temperature was not measured, since the only comparisons in the current study were between the control and propranolol-treated forearms during a single bout of exercise. Thus core temperature was identical for both forearms during data collection and, thus, could not account for any differences in the responses. The sweat collected in each Macroduct was determined using a volumetric technique, and forearm sweat rate was expressed in milligrams per square centimeter per minute. The Macroducts were then removed, and the number of active sweat glands was counted by the same nonblinded investigator throughout the study and expressed in glands per square centimeter.

It has been shown that propranolol very effectively blocks the β-adrenergic receptors of the human sweat gland but does not affect cholinergic sweating (8, 23). For example, Behm et al. (2) reported that propranolol completely blocked isoproterenol-induced sweating in the forearms of control and cystic fibrosis heterozygote subjects. This was qualitatively confirmed in the current study prior to the start of data collection, as evidenced by the failure of isoproterenol to produce any measurable sweating response following propranolol iontophoresis for up to 30 min.

Paired t-tests were used to compare the data obtained from the control vs. the propranolol-treated forearm. Significance was set at P < 0.05.

RESULTS

The sweat rate for the control and propranolol-treated forearm was 0.62 ± 41 and 0.60 ± 0.44 (SD) mg·cm⁻²·min⁻¹, respectively (Fig. 1). No significant difference [P = 0.86, 95% confidence interval (CI₃) = −0.13 to 0.15] was found between the means. The density of active sweat glands for the control and propranolol-treated forearm was 130 ± 6 and 134 ± 5 (SD) glands/cm², respectively (Fig. 2). No significant difference (P = 0.33, 95% CI₃ = −4.01 to 6.43) was found between
the means. End-exercise skin temperature was 32.9 ± 0.2 and 33.1 ± 0.3°C for the control and propranolol-treated forearm, respectively (*P* = 0.51). The male and female subjects responded similarly; thus the data were pooled for all 14 subjects.

**DISCUSSION**

The most important findings of the current study were that propranolol iontophoresis had no effect on forearm sweat rate or the number of active sweat glands during exercise. Although such findings do not agree with numerous previous studies that have examined sweat rate following the oral administration of propranolol (10, 13, 17, 18, 31), they are supported by results of two previous studies in which propranolol was administered locally. Sato and Sato (22) examined the in vitro pharmacological responsiveness of cannulated monkey palm eccrine sweat glands. They reported that increasing the concentration of methacholine, a cholinergic agonist, in the circulating water bath caused a hyperbolic increase in sweat rate from the isolated glands. The subsequent addition of propranolol had no effect on the methacholine-induced sweat rate. Similarly, Foster et al. (8) found that intradermal injections of acetylcholine into the forearms of six resting male subjects caused a rapid increase in sweat rate, as measured using a ventilated capsule. The cholinergic sweat responses, however, were not affected by propranolol injected before or simultaneously with acetylcholine. Thus both of these studies (8, 22), which used methodologies that eliminated the confounding systemic effects of oral propranolol administration, strongly support the findings of the current study.

A review of the literature shows that the effect of propranolol on sweating during exercise is controversial. A likely cause for the divergent results is that the oral administration of propranolol is known to have a variety of systemic effects, many of which can affect sweating in opposite directions. For example, Freund et al. (9) exercised 14 male subjects in the heat for 90 min following placebo and oral propranolol administration. They reported that propranolol increased sweat rate by 10.3%. However, it is difficult to determine the physiological mechanism responsible for the increase in sweat rate in their study, since oral propranolol administration also simultaneously increased core temperature, which is known to increase sweating, and decreased mean skin temperature and mean arterial blood pressure, both of which have been shown to decrease sweating (7, 14). Similarly, Pescatello et al. (17) found that oral propranolol administration significantly reduced the slope of the chest sweat rate-esophageal temperature relationship, yet there was no change in the whole body sweat rate during exercise. To reconcile these divergent findings, they hypothesized that the reduced sweat rate-esophageal temperature relationship was offset by a higher core temperature; consequently, the whole body sweat rate during exercise was not different between the propranolol and placebo trials. These examples clearly illustrate that the confounding systemic effects associated with oral propranolol administration made it extremely difficult for past researchers to determine the direct effect of propranolol on sweat rate during exercise. To overcome this issue, the current study used propranolol iontophoresis to eliminate the confounding systemic effects associated with the oral administration of propranolol, thus allowing for the determination of the direct effect of β-adrenergic receptor blockade on sweating during exercise.

Furthermore, the results of the current study extend the findings of two recent studies (3, 15). Mora-Rodriguez et al. (15) approached the topic from a different methodological perspective when they measured sweat rate during exercise in the heat following intravenous infusion of saline, epinephrine, or glucose. Compared with the saline trial, glucose infusion significantly reduced the rise in plasma catecholamines during exercise, while epinephrine infusion significantly increased it. The sweat rate, however, was the same during all three trials, suggesting that removal of β-adrenergic stimulation during the glucose infusion trial did not, in and of itself, attenuate cholinergic sweating. Buono et al. (3) used the reverse approach of the current study to investigate the potential role of in vivo β-adrenergic stimulation on sweat production during exercise. They used atropine iontophoresis to block the cholinergic component of sweating, thus isolating any potential β-adrenergic response. They found no measureable sweat production during exercise in the skin pretreated with atropine. They concluded that in vivo β-adrenergic stimulation alone is not sufficient to elicit sweat production in exercising humans. Clearly, the results of Mora-Rodriguez et al. and Buono et al. question the importance of in vivo β-adrenergic stimulation on sweat production during exercise. The results of the current study showing that localized β-adrenergic receptor blockade does not affect sweat production during exercise support their findings (3, 15). Taken together, the data of all three studies strongly suggest that sweating during exercise is predominantly if not exclusively, controlled via the cholinergic system. Thus, further work is warranted to identify the physiological importance of the dual cholinergic and adrenergic innervation in human sweat glands (21, 24, 28).

**Perspectives and Significance**

A review of the literature shows that the effect of propranolol on sweating during exercise is controversial. A likely cause for the divergent results is that the fact the oral administration of propranolol is known to have a variety of systemic effects, many of which can affect sweating in opposite directions. The results of the current study show that when propranolol is administered locally, thus eliminating the confounding systemic effects of the drug, it does not directly affect eccrine sweating during the initial stages of high-intensity exercise in young, healthy subjects. Such results support previous reports that sweating during exercise is predominantly controlled via the cholinergic system.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**REFERENCES**


