

# Carl V. Gisolfi, Ph.D., and his career in thermoregulation

By Charles M. Tipton



Carl V. Gisolfi. Photo courtesy of Kevin C. Kregel

## Introduction

Carl V. Gisolfi (1942-2000) was a Distinguished Professor of Exercise Science and Physiology and Biophysics at the University of Iowa who received a B.S. degree in Physical Education from Manhattan College in 1964 and his Ph.D. in Physiology from Indiana University in 1969. His advisor was Professor Sid Robinson (1902-1982) who was the first graduate student mentored by Professor David Bruce Dill (1891-1986) when Dill was the director of research activities conducted at the Harvard Fatigue Laboratory. Gisolfi was extremely proud of his thermal linkage to these renowned investigators and designed his climatic laboratory at Iowa with them in mind.

During the early years in Iowa City, he conducted predominately human thermal investigations. Although this trend continued throughout his 31 years at the university, he expanded his focus to include primates and rodents while exploring system, cellular and molecular relationships between thermal stress and gastrointestinal functions. Although human and animal studies were integrated throughout his career, for purposes of this presentation they will be discussed separately.

## Human studies

In the 1970's he conducted a running study with Copping (75% of maximum oxygen consumption,  $VO_2$  max) in the heat (33.5/21.5°C, dry bulb/wet bulb) that resembled the classic desert marching study of Pitts and associates in that the rise in rectal temperature was closely related to the percentage of water being lost. In addition they found it made no difference whether cold or warm water replaced the fluid being lost; that the consumption of fluid during the run was more effective in reducing a rise in rectal temperature than consuming a similar volume 30 minutes before the run and that "sponging off" with a cold towel was ineffective in preventing the rise in core temperature. Interestingly, this study was selected by the editor of the *Medicine and Science in Sports and Exercise* (Buskirk) as the most influential one during his tenure. With colleagues, they demonstrated for both men and women that interval training in a cool environment (21°C) for 8-11 weeks would account for 50% of the thermal adjustments associated with heat acclimation, and that such individuals could maintain thermal equilibrium during moderate work for as long as 4 hours. This type of acclimation was independent of aerobic capacity and dependent upon maintaining a continuous elevated rectal temperature. In a related study with women who used an interval training program for the same duration (4 hours) at a similar temperature, they were able to improve their work-heat tolerance at 45/24°C (dry bulb/wet bulb) conditions whereas a control and untrained group that were exposed to these same temperatures for 8 days were unable to show evidence of acclimation.

When a controversy existed between the advantages of consuming either a carbohydrate-electrolyte beverage or water when exercising in the heat, his laboratory investigated the matter by having subjects exercise (60%  $VO_2$  max) for 3 hours while drinking both beverages on two different trials. They also drank for 3 hours while recovering in the heat. Measurements of heart rates, sweat rates or rectal temperature during exercise showed no significant differences that could be attributed to the beverages, whereas the perceived exertion score was higher with water consumption. During recovery, consumption of the carbohydrate-electrolyte beverage was associated with more volume being consumed, a higher plasma volume value, elevated osmolarity levels, increased glucose concentration, and a higher body weight when compared to the consumption of water. All differences noted were statistically significant. They concluded that a carbohydrate drink was as effective as water during the exercise and more effective during the recovery process. Subsequently, they examined the magnitude of gastric emptying while exercising (3 hours at 60%  $VO_2$  max) in the heat (33°C) after consuming water or a variety of beverages that contained glucose, a glucose polymer, or a glucose polymer combined with fructose. Measurements of heart rates, sweat rates, rectal and mean skin temperatures and plasma electrolyte concentrations exhibited no meaningful differences between the groups. Although plasma volume differences prevailed among the trials, none had statistical significance. The gastric residual volumes at the end of exercise were similar among the groups but the glucose solution had higher residuals than the water trial. The take home message was that during prolonged exercise in the heat, 90% of the ingested beverage, whether water or a carbohydrate solution, can be emptied from the stomach to reduce the effects of dehydration.

Gisolfi and colleagues at the University of Iowa became involved in the controversy as to whether tympanic membrane temperatures were representative of core body temperatures. After modifying the tympanic membrane probe and placement they found a consistent response with facial cooling; that it had a faster response to foot warming than an existing esophageal temperature probes, and that it warranted being considered as a standard for the determination of core body temperature. In the late 1980's and early 1990's, his laboratory became very interested in the various aspects of heat stress, particularly, the role of exercise in the production of heat shock proteins in humans and of the role of these stress proteins in providing tolerance for thermal conditions which markedly elevate core rectal temperatures. In fact his study with Mosely was the first to indicate that heat shock protein-70 (HSP-70) could be produced in humans exercising in the

heat, and that HSP-70 could be a useful marker of the cell's thermal history and of thermal tolerance. As estrogen supplementation will enhance thermoregulatory responses in premenopausal women while improving HSP-70 synthesis during exercise in the heat, his laboratory plus Mosely investigated the effects of 3 days of estrogen supplementation on thermoregulatory responses during exercise in premenopausal women during the follicular phase of their menstrual cycles. Surprisingly, they found that 3 days of estrogen supplementation had no significant effect on the synthesis of HSP-70, nor on the threshold for sweating, the threshold for the appearance of forearm blood flow, the heat transfer to the skin, or the heat dissipation by evaporative cooling.

## Animal studies

Gisolfi was impressed by the 1938 human study of Marcus Nielsen which demonstrated a linear relationship between work rate and the rise in body temperature that occurred during graded steady state exercise, which indicated that the rise in body temperature could be used as an indicator of work intensity. Since Young and colleagues had demonstrated similar trends had occurred in dogs, Gisolfi measured colonic and tail-skin temperature in rats running at different speeds to determine whether the same relationship applies to this species. Although rats could achieve thermal balance during exercise, the authors did not find a meaningful relationship between the rise in colonic temperature and work rate. With Fruth, rats were endurance trained in a cool (23°C) environment before they and non-trained controls were exposed to an exhaustive exercise test in the heat which elevated colonic temperatures higher than 41.6°C. The trained group not only had a significantly lower mortality rate, they exhibited a lower serum transaminase concentration (less tissue damage) than their non-trained controls.

Gisolfi and Christman perfected stereotaxic techniques for rats that enabled them to inject norepinephrine (NE) into the preoptic/anterior hypothalamic region. They found that repeated injections increased heat dissipation during rest and exercise. When the animals received NE while resting and during exercise in the heat, only the resting animals exhibited evidence for an increased hypothalamic sensitivity to NE. It was not clear why this effect did not occur with the exercising animals. Splanchnic vascular resistance is progressively increased in humans with hyperthermia. Consequently, Kregel and Gisolfi investigated in rats the role of the sympathetic nervous system in the process using direct measurements of splanchnic sympathetic nerve activity (SSNA). From pressure and temperature measurements, they confirmed the elevation in colonic temperature that occurs with the splanchnic vascular constriction of hyperthermia was intimately linked to increased SSNA. Furthermore, they demonstrated the splanchnic vasodilation that occurs when colonic temperatures exceeds 41°C was not the result of decreased SSNA or concentrations of circulating catecholamines, and speculated it was the result of hyperkalemia.

Besides rats, his laboratory utilized primates in their thermal studies and were successful in developing a primate exercise chair apparatus that, when used with a food reward, was capable of elevating heart rates by 120 beats per minute, increasing respiratory rates by 24 breaths per minute, raising colonic temperature by 1.2°C during a 30 minute period. The chair was incorporated in a study comparing the sweating profiles of patas and rhesus monkeys as measured from palmar, chest and lateral calf regions when external temperatures were 40°C. Since at any given colonic or skin temperature sweating was 2-6 fold higher in patas than in rhesus monkeys, they concluded the patas monkey was the model of choice to study human sweating. They inserted thermocouples into four thermodes which were then implanted into four hypothalamic sites of patas monkeys. The thermodes were perfused with water ranging in temperature from 37.0 to 41.0°C, which increased hypothalamic temperatures from 37.2 to 39.5°C while increasing chest sweating rate by 600%. Mean skin temperature exhibited minimal changes during the perfusion process.

Unexpectedly, chest sweating rate increased when the animal struggled within the restraining chair causing elevations in heart rates of ~50 beats per minute. They concluded sweating in patas monkeys was controlled by peripheral and central thermal inputs as well as by nonthermal factors.

Patas monkeys were also used by Sato and Gisolfi to study the effects of 9 weeks and 9 months of heat acclimation (33°C) on the in vivo and in vitro functions of sweat glands located on the lateral region of the calf. Nine weeks of acclimation resulted in lower skin and rectal temperatures as well as significant increases in maximal sweat rates as induced by infusions of methacholine (MCH). Long term acclimation was associated with a significant enlargement of sweat gland size as determined by tubular length and volume and with increased in vitro maximal sweat rates as determined from MCH infusions. In addition, acclimation was identified with a greater volume of sweat-per-unit length of the secretory coil. They concluded acclimation resulted in larger and more efficient sweat glands that were capable of producing a higher sweat volume during heat stress situations.

Gisolfi was stimulated by Robinson to seek an explanation for the regulated rise in central body temperature with exercise and intrigued by the 1970 theory of Myers and Veale that proposed the set point for body temperature in the mammal was governed by the balance between extracellular sodium and calcium ions within the posterior hypothalamus. He sought collaborations with Meyers, Phillips and Mora and began systematic investigations in animals with intracerebroventricular administration of artificial cerebrospinal fluid, which entered the posterior hypothalamic regions via the third ventricle. In early experiment with rats, excessive calcium was perfused during rest and exercise. They found significant decreases in colonic temperatures during resting and exercise conditions, but with only limited changes in skin temperatures. These results were attributed to the increased binding of calcium by the hypothalamus and to an enhanced cutaneous blood flow. Uncertain about the role of calcium in altering the set point, he led a comprehensive study that included central infusions of artificial cerebrospinal fluid containing different calcium concentrations at different colonic temperatures. They found that an elevated calcium concentration (1) at 15°C, was unable to elicit vasodilation; (2) at 22°C, did not initiate sweating; (3) was unable to stimulate sweating ; and (4) at either 35 or 40°C, was unable to lower colonic temperature. Hence, they concluded the data argued against “a set-point function for this cation.” Increased plasma osmolality will decrease the rate of sweating during thermal stress. To determine whether this effect was related to the sodium concentration or to the osmolality of the perfusate, he infused artificial cerebrospinal solutions into the third ventricle of heat-stressed primates that had the same osmolality (~800 mosmol/kg), but differed in tonicity (NaCl vs sucrose). The sucrose-containing perfusate had no significant effect on calf sweating rates or colonic temperatures whereas the NaCl perfusate decreased primate sweating rates by 53% while being associated with elevated colonic temperatures during recovery from the heat stress. They concluded the presence of increased sodium within the artificial cerebrospinal fluid was more responsible for heat loss than osmolality per se. To determine whether the neuropeptides arginine vasopressin (AVP) and angiotensin-II (ANG-II) were contributing to the reduction in heat loss, they included these neuropeptides with the perfusions into the third cerebral ventricle of primates. ANG-II was associated with a decreased mean sweat rate, which suggested it was a contributor, especially when dehydration was present; however, this was not the case with AVP.

Later, his laboratory began to explore the relationship between heat stress and the endotoxemia of heat stroke. This interest, which included hyperemia and circulatory failure, led to a productive collaboration with Pope Mosely, M.D., that continued to his untimely death. One of their initial studies was to determine, with rats, whether acute exposure to a sub lethal heat stress (42.5°C) would provide acquired resistance to a lethal dose of bacterial endotoxin, or lipopolysaccharide (LPS). They (with Ryan & Flanagan) conducted experiments with heated and non-heated rats that received either saline or lethal doses of LPS. The results indicated that more than 70% of the non-heated rats died from shock after infusion of LPS, whereas all rats exposed to

an acute heat stress had survived. Since blood levels of LPS in the heat-stressed rats were undetectable, they effectively demonstrated that prior acute heat exposure could have a protective effect against bacterial LPS.

As noted previously, Kregel and Gisolfi were among the first to show severe hyperthermia would cause a selective loss of splanchnic vasoconstrictor tone, which preceded the onset of endotoxemia and circulatory collapse. To gain insights on responsible mechanisms, Gisolfi, Hall and Buettner utilized electron paramagnetic resonance spectroscopy on rat portal venous blood obtained from heat stressed animals. They found three species were present when the colonic temperature exceeded 39°C. One was the copper binding protein ceruloplasmin, another was a semiquinone free radical, while the third was a nitric oxide (NO)-heme complex. These results were the first to demonstrate hyperthermia could produce the presence of a free radical and NO-heme complex in the blood. They were also the first to suggest a thermo-protective role for NO.

Follow up studies by Hall, Gisolfi and members of the Iowa Free Radical Research Institute demonstrated that hyperthermia in rats was associated with the appearance of hypoxic cells in the liver and small intestines and strongly suggested they were the sources for the reactive oxygen and nitrogen species that were detected. These same investigators subsequently developed a complex, integrative hyperthermia model to explain the cascade of systematic and cellular events that occur from the time of heat exposure to the time of circulatory collapse. From their multiple experimental interventions with hyperthermic animals, they concluded nitric oxide synthase activity was necessary for heat tolerance to occur, whereas an overproduction of nitric oxide appeared to trigger the splanchnic vasodilation that preceded vascular deterioration. They also felt hyperthermia resulted in elevated cellular xanthine oxidase production, which hastened circulatory and intestinal barrier dysfunction because of an increased production of reactive oxygen species.

The study that was published after his death included Lambert, Berg, Mosely, Oberley plus Kregel and pertained to intestinal permeability being measured during in vivo and in vitro conditions. The in vivo conditions effectively demonstrated that intestinal permeability was markedly enhanced at a colonic temperature of 42.5°C when compared to results obtained at colonic temperatures of 37, 41, or 41.5°C. The in vitro studies used everted sacs, and negative results were found when measurements were made to determine the presence or changes in reactive oxygen and nitrogen species. Since the histological findings showed elevated temperatures caused intestinal epithelial damage, the authors suggested that the thermal disruption of epithelial membranes were associated with intestinal barrier dysfunction.

Just prior to his death, Gisolfi received and corrected proofs of his text with Mora entitled "The Hot Brain." If he had survived to the present time (2010), one could easily speculate that his next book would have been labeled as "The Hot Gut."

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