Broiler Survivors of Intravenous Micro-Particle Injections: Evaluation of Growth, Livability, Meat Quality, and Arterial Blood Gas Values During a Cyclic Heat Challenge[1]

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ABSTRACT When broilers are exposed to high ambient temperatures, their cardiac output can increase by 20 to 50%. Previously, we developed an intravenous micro-particle injection technique to select broilers having a cardiopulmonary capacity capable of accommodating increases in cardiac output associated with fast growth and cool temperatures. In the present study, male broilers were injected at 18 to 20 d of age with cellulose micro-particles sufficient to trigger >50% mortality by 35 d of age. The survivors of micro-particle injections (cellulose survivors) and saline-injected flock mates (control group) were exposed to a moderate cyclic heat challenge (peak temperature of 35 to 37°C) beginning on d 36 and continuing through d 57. We tested the hypothesis that if the cellulose survivors represent the population cohort having the most robust cardiopulmonary capacity, then during a subsequent heat challenge these survivors potentially may perform better than their unselected flock mates. Based on data combined from two independent experiments, the cellulose survivors exhibited improved livability and body weight gain when compared with their unselected flock mates during the cyclic heat challenge. Meat quality characteristics did not differ between the groups. In a third experiment, cellulose survivors and saline-injected male broilers were reared at thermoneutral temperatures or were exposed to a cyclic heat challenge beginning on d 36. Arterial blood samples were collected from unanesthetized birds at 47 to 49 d of age and were analyzed for pH, partial pressure of CO_2, bicarbonate, partial pressure of O_2, and saturation of hemoglobin with O_2. The blood gas values for the cellulose survivors and saline-injected broilers did not differ within a temperature regimen, regardless of whether the broilers were chronically acclimated to heat or were exposed to an acute heat challenge at the end of the experiment. The cellulose survivors did not differ in susceptibility to panting-induced respiratory alkalosis or hypoxemia when compared with their saline-injected flock mates. Overall, these observations indicate that selection for a robust cardiopulmonary capacity can confer advantages in growth and livability without affecting meat quality when broilers are exposed to a moderate heat challenge.

(*Key words*: alkalosis, ascites, broiler, heat stress vascular occlusion)

2003 Poultry Science 82:484–495

INTRODUCTION

When previously non-acclimated domestic fowl are exposed to high environmental temperatures, integrated cardiopulmonary responses are initiated that enhance short-term viability by accelerating the rate of heat dissipation. As the body temperature rises, arterioles supplying the organs and tissues that participate in heat elimination (upper respiratory passageways, respiratory muscles, skin) dilate to increase blood flow and heat transfer. This vasodilation is sufficient in magnitude to cause an overall reduction in total peripheral resistance and a corresponding reduction in the mean systemic arterial pressure. To counteract the excessive outflow of blood from the arterial pressure reservoir, total peripheral resistance is partially restored through reflex constriction of blood vessels supplying the visceral organs. In addition, increases in heart rate and venous return support an overall increase in the cardiac output that more rapidly refills

Received for publication August 26, 2002.

Accepted for publication October 21, 2002.

[1]U.S. patent pending (File No. 09-013,774) protects the exclusive rights of the University of Arkansas and Hubbard ISA to all uses of the intravenous micro-particle injection technology within the context of evaluating or affecting pulmonary vacular capacity, pulmonary vascular resistance, pulmonary hypertension, cardio-pulmonary hemodynamics, and susceptibility to pulmonary hypertension and pulmonary hypertension syndrome (ascites) in domesticated animal species.

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Abbreviation Key: HbO_2 = saturation of hemoglobin with O_2; HCO_3 = bicarbonate; L* = lightness value; $PaCO_2$ = partial pressure of CO_2 in arterial blood; PaO_2 = partial pressure of O_2 in arterial blood; PHS = pulmonary hypertension syndrome.

the arterial pressure reservoir and prevents further reductions in arterial pressure (Frankel et al., 1962; Weiss et al., 1963; Whittow et al., 1964; Richards, 1970; Wolfenson et al., 1981; Wolfenson, 1986; Darre and Harrison, 1987; Zhou, 2000). Respiratory mechanisms such as gular fluttering and thermal polypnea (panting) increase the ventilation of moist surfaces in the nasal and buccal cavities and conducting airways (anatomical dead space), thereby increasing heat dissipation through evaporative cooling. Panting also unavoidably hyperventilates the pulmonary gas exchange surfaces and partially overrides the respiratory control systems that normally stabilize the pH and partial pressure of CO_2 in arterial blood ($PaCO_2$). Consequently, an increase in blood pH caused by a reduction in the $PaCO_2$ (respiratory alkalosis) consistently develops when non-acclimated domestic fowl begin to pant (Brackenbury et al., 1981; Wolfenson et al., 1981; Arad and Marder, 1983; Bottje and Harrison, 1985a; Pinshow et al., 1985; Wolfenson, 1986; Barnas and Rautenberg, 1987; Darre and Harrison, 1987; Beers et al., 1989; Marder and Arad, 1989; Gonet et al., 2000; Yahav, 2000; Sandercock et al., 2001). Susceptibility to severe respiratory alkalosis has been proposed as a major factor contributing to poor production performance and increased mortality during heat stress (Bottje and Harrison, 1985b; Beers et al., 1989; Marder and Arad, 1989; Yahav et al., 1995; Gonet et al., 2000).

Theoretically the cardiopulmonary responses to heat stress might be affected when broiler lines are genetically selected to reduce their susceptibility to pulmonary hypertension syndrome (PHS, ascites). Susceptibility to PHS has been attributed to a cardiopulmonary capacity that is inadequate to accommodate increases in cardiac output associated with fast growth and cool temperatures. Sires and dams whose robust cardiopulmonary capacity enabled them to survive surgical occlusion of one pulmonary artery subsequently produced progeny that exhibited a 75% reduction in PHS susceptibility within two generations of selection (Wideman and Bottje, 1993; Wideman et al., 1997; Wideman and French, 1999, 2000; Wideman, 2001). During early pathogenesis leading to PHS, susceptible broilers maintain a higher pulmonary arterial pressure, pulmonary vascular resistance, $PaCO_2$, and cardiac output; a lower partial pressure of oxygen (PaO_2) and saturation of hemoglobin with O_2 (HbO_2) in arterial blood; and a more acidic blood pH when compared with PHS resistant or clinically healthy broilers. The physiological advantages contributing to PHS resistance therefore appear to include a robust pulmonary vascular capacity coupled with the attenuation of an intrapulmonary diffusion limitation that otherwise tends to retard adequate O_2 and CO_2 equilibration when the lungs are challenged with a disproportionate increase in cardiac output (Wideman and Tackett, 2000; Wideman et al., 2000; Chapman and Wideman, 2001; Wideman, 2000, 2001). Exposure of previously non-acclimated broilers to high ambient temperatures causes a 20 to 50% increase in cardiac output (Whittow et al., 1964; Darre and Harrison, 1987). Heat-induced increases in cardiac output theoretically should be better tolerated at lower pulmonary arterial pressures and with less right ventricular work by broilers having superior cardiopulmonary capacities. In contrast, if selection for PHS resistance also increases the efficiency of pulmonary blood-gas equilibration or enhances the sensitivity or responsiveness of blood gas regulatory systems, then the resistant broilers could be more susceptible to severe respiratory alkalosis or may experience increased mortality due to a reduced ability to utilize evaporative cooling during heat stress. For example, heat-stressed domestic fowl may be prevented from maximizing their rates of evaporative cooling if declining $PaCO_2$ values and an alkaline blood pH are detected by chemoreceptors capable of exerting profound restraint on further increases in respiratory minute ventilation (Osborne et al., 1977; Mather et al., 1980; Fedde et al., 2002).

Recently an intravenous micro-particle injection procedure was developed as an efficient, non-surgical alternative to unilateral pulmonary artery occlusion. The injected micro-particles are carried to the lungs by the venous blood, where the precapillary arterioles become obstructed in proportion to the numbers and sizes of the particles injected. Relatively low doses of cellulose microparticles injected i.v. into male broilers caused PHS, whereas higher injection doses triggered substantial levels of acute mortality within 24 h. Broilers from PHS-resistant lines exhibited much lower incidences of mortality at 24 h post-injection than broilers from PHS-susceptible or unselected lines (Wideman and Erf, 2002; Wideman et al., 2002). These observations are consistent with the hypothesis that susceptible broilers have a limited pulmonary vascular capacity and succumb to levels of microvascular obstruction that can be better tolerated by resistant broilers having more robust pulmonary vascular capacities (Wideman, 2001; Wideman et al., 2002). In the present study, broilers were injected at 18 to 20 d of age with micro-particle dosages sufficient to trigger substantial 24 h post-injection mortality. Immune-mediated clearance of entrapped cellulose micro-particles restores patency to the pulmonary vasculature of the surviving birds within 17 d post-injection (Wideman et al., 2002). If the broilers surviving to 35 d of age in the present study represent the population cohort having the most robust cardiopulmonary capacity, then during a subsequent heat challenge these survivors potentially may exhibit improved livability, growth performance, and meat quality when compared with their unselected (saline-injected) flock mates as long as the advantages of a superior cardiopulmonary capacity override any potential enhancement of respiratory alkalosis or chemoreceptor restraint on evaporative cooling. A cyclic rather than a constant heat challenge was imposed because cyclic temperatures are more typically encountered during commercial broiler growout, and the cool portion of the cycle provides an opportunity for increased feed and water consumption to support growth (Mueller, 1961; Bottje and Harrison, 1985b; Smith and Teeter, 1987; Whiting et al., 1991a; May and Lott, 1992; Yahav et al., 1996). Meat quality also was evaluated because heat stress has been associated with lactic acidosis,

increased water-holding capacity of the carcass during ice-water chilling, lower oven-cooked fillet yield, and increased paleness (pale, soft-exudative-like lesions) (Frankel and Frascella, 1968; Beers et al., 1989; Whiting et al., 1991b; Sandercock et al., 2001).

MATERIALS AND METHODS

Bird Management

Male broiler chicks from a commercial hatchery[3] were transported on the day of hatch (d 1; October 22, 2001; January 28, 2002; and April 25, 2002, for experiments 1, 2 and 3, respectively) to the Poultry Environmental Research Laboratory at the University of Arkansas Poultry Research Farm. The chicks were wing-banded and randomly assigned to the front or back half of environmental chambers (8 m^2 floor space) that were divided by a center divider. They were brooded on fresh litter at 33°C on d 1 to 5, 29°C on d 6 to 10, 27°C on d 11 to 17, and 22 to 24°C through d 35. They were fed a 23% CP corn-soybean meal-based broiler ration formulated to meet or exceed the minimum NRC (1994) standards for all ingredients. Feed and water were provided for consumption ad libitum. The feed was provided as crumbles for the first 7 d and as pellets thereafter. Water was provided in Plasson (bell-type) waterers. Lights were on for 24 h/d through d 5 and for 23 h/d thereafter.

Experiment 1

Four environmental chambers containing approximately 110 broilers per chamber were used for this experiment. Immediately prior to injection, Microgranular CM-32 ion exchange cellulose[4] (30-μm average maximum particle dimension) was suspended at 0.02 g/mL in normal saline (9 g NaCl/L distilled water) containing 150 U ammonium heparin[5]/mL. The cellulose was maintained in uniform suspension by continuous stirring on a magnetic stirring plate. The suspension was drawn into a 1-mL tuberculin syringe through an attached 22-ga needle for injection into unanesthetized broilers via the basilica (wing) vein. Initial dosage assessments were conducted by injecting groups of 10 chicks with 0.4, 0.5, 0.6, or 0.7 mL of the 0.02 g/mL cellulose suspension on d 16, and the respective 24 h post-injection mortalities were 3/10, 8/10, 8/10, and 9/9 (one bird was misinjected). On d 18, 36 birds per chamber were injected with 0.8 mL heparinized saline alone (saline group), and the remaining birds were injected with 0.45 mL of the cellulose micro-particle suspension (cellulose group). Ten birds were culled due to misinjections. Saline-injected birds were returned to one-half of each chamber (alternating front or back), and cellulose-injected birds were placed in the remaining chamber halves. The 24 h post-injection mortality was recorded, as well as the mortalities for d 19 to 35. Ascites was diagnosed only when ascitic fluid accumulation was evident or when a fibrin clot adhered to the surface of the liver. The bird density was reduced on d 34 to leave 30 to 31 of the largest birds per chamber half. On d 36, individual body weights were recorded, and feed was weighed-in by chamber half. The moderate cyclic heat challenge initiated on d 36 included 16 h/d at 35°C (95°F); 6 h/d at 23°C (74°F), and 2 h/d of transitional temperatures. Relative humidity was not monitored. Birds that died between d 36 and 57 were weighed and necropsied to determine whether the mortality was due to ascites (ascites mortality) or other causes (pooled as nonascitic mortality). All survivors on d 57 were euthanized with CO_2 gas, weighed, and evaluated for ascites. Feed remaining on d 57 was weighed to determine the net feed consumption by chamber half.

Experiment 2

Five environmental chambers containing approximately 112 broilers per chamber were used in this experiment. Microgranular CM-32 ion exchange cellulose[3] was prepared and injected as described above. On d 18 and 19, all birds were weighed, approximately 33 birds per chamber were injected with 0.45 mL heparinized saline alone (saline group), and the remaining birds were injected with 0.40 mL of the cellulose micro-particle suspension (cellulose group). Three birds were culled due to misinjections. Saline-injected birds were returned to one-half of each chamber (alternating front or back), and cellulose-injected birds were placed in the remaining chamber halves. The 24 h post-injection mortality was recorded, as well as the d 19 to 35 ascitic and nonascitic mortality. On d 36 the bird density was reduced to 28 birds per chamber half, body weights were recorded, and feed was weighed-in by chamber half. The moderate cyclic heat challenge initiated on d 36 included 16 h/d at 37°C (98°F), 6 h/d at 23°C, and 2 h/d of transitional temperatures. Relative humidity was not monitored. Birds that died between d 36 and 57 were weighed and necropsied to determine whether the mortality was due to ascites. All survivors were weighed and necropsied, and the feed remaining was weighed.

To assess meat quality characteristics, 10 birds from each chamber half were processed (n = 50 per treatment). Feed was withdrawn 10 h prior to slaughter; however, birds were allowed free access to water during the withdrawal period. One hour prior to slaughter, birds were transported in coops to the University of Arkansas Pilot Poultry Processing Plant. Birds were hung on a shackle line and commercially processed in order to evaluate postmortem pH, meat color, drip loss, and cook loss. Birds were electrically stunned (11 V, 11mA, 10 s), manually cut (severed left carotid artery and jugular vein), bled out (1.5 min), scalded (55°C, 2 min), and picked in-line using commercial defeathering equipment. Birds were eviscerated and placed in prechill for 15 min (12°C) and a chill

[3]Hubbard ISA, Hot Springs, AR.
[4]Fisher Scientific, St. Louis, MO.
[5]Sigma Chemical Co., St. Louis, MO.

tank for 45 min (2°C). Carcasses were then stored on ice in a 4°C cooler until further analysis. Breast fillets were deboned at 4 h postmortem. Breast samples were collected from the right fillet of each bird at 0.25, 1.25, 2.5, 4.0, and 6.0 h postmortem for pH analysis. The samples were immediately packaged in plastic bags, frozen in liquid nitrogen, and stored at –76°C until analysis. Muscle pH was determined using the iodoacetate method as described by Sams and Janky (1986). The weights of the left fillets were recorded at 4 and 24 h postmortem to determine drip loss (%). At 4 and 24 h postmortem, lightness (L*) values were measured on the left breast fillets using a Minolta colorimeter.[6] The left fillets were aged on ice until 24 h postmortem and were then weighed and baked at 177°C on raised wire racks in aluminum-lined and -covered pans in an convection oven to an internal endpoint temperature of 76°C. Fillets were then cooled to room temperature and weighed again to determine the cook loss.

Experiment 3

Broilers were reared in four environmental chambers as described above, and were injected at 20 d of age with 0.45 mL heparinized saline alone (saline group, n = 80, 20 per chamber), or with 0.40 mL of the cellulose microparticle suspension (cellulose group, n = 200, 50 per chamber). The mortality at 24 h post-injection was recorded, as well as the d 19 to 35 ascitic and nonascitic mortalities. Two chambers were held at a constant thermoneutral temperature of 24°C (75°F) throughout the experiment (thermoneutral treatment), and a moderate cyclic heat challenge (16 h/d at 35°C or 95°F, 6 h/d at 24°C, and 2 h/d of transitional temperatures) was initiated in two chambers on d 36 (cyclic heat treatment). Body weights were recorded only for the birds that were used for blood gas experiments. Large, clinically healthy broilers from all four chambers (15 per group) were used for blood gas analyses on d 47 to 49. Birds were restrained unanesthetized on their right sides, and the left wing was extended laterally to expose the ventral surface. Lidocaine (2%) was injected into the skin and muscle surrounding the brachial artery, and then this vessel was isolated and cannulated with a 20-cm length of PE-50 polyethylene tubing filled with heparinized saline (200 U/mL in 0.9% NaCl). The tip of the cannula was advanced approximately 6 cm from its point of insertion, sutured to the blood vessel, flushed with 2 mL heparinized saline, and knotted at the distal end. Cannulated broilers were placed in an open mesh basket in an upright posture and returned to their original environmental chamber for 30 min. An initial 1 mL of arterial blood sample was collected with minimal disturbance to the bird. The knot at the end of the cannula was cut off, and arterial blood pressure forced the saline out of the cannula; then the tip of a 23-ga needle attached to a 1-mL tuberculin syringe was inserted into the cannula to anaerobically withdraw the blood. Dead spaces in the needle and syringe hub previously had been filled with heparinized saline. Birds in the cyclic heat treatment then were transferred to a thermoneutral (24°C) environment, and additional blood samples were collected 30 and 60 min thereafter. Birds in the thermoneutral treatment were transferred to a hot (35°C) environment, and additional blood samples were collected 30 and 60 min thereafter. All arterial blood samples had a maximum volume of 1 mL, and no blood replacement was administered. The arterial cannulae were flushed with fresh heparinized saline and reknotted after each sample collection. All samples were injected within 60 s after collection into a Radiometer ABL 330 Acid-Base Laboratory.[7] In addition to relying on one- and two-point automatic internal recalibration of the ABL 330 at 2- and 4-h intervals, respectively, appropriate functioning of the blood gas analyzer was assessed by periodically injecting Blood Gas Qualicheck reference standards.[6] The pH, PCO_2, and PO_2 values for the acidemic, normal, and alkalotic Qualicheck standards, respectively, averaged (mean ± SEM, n = 18): pH 7.155 ± 0.004, pH 7.395 ± 0.002, and pH 7.639 ± 0.003 (≤0.1% CV for each standard); PCO_2 = 56.3 ± 0.5, 38.1 ± 0.3, and 17.9 ± 0.3 mm Hg (≤3% CV for each standard); and, PO_2 = 54.2 ± 0.9, 111.2 ± 0.6, and 175.7 ± 1.6 mm Hg (≤4% CV for each). These Qualicheck values confirmed the ABL 330 functioned reproducibly over the recommended range.

The primary blood values for pH, $PaCO_2$, and PaO_2 were generated by the blood gas analyzer operating at a sample chamber temperature of 37°C and were recalculated by the ABL 330 for a temperature of 41°C to match the normal body temperature of domestic fowl (Fedde, 1986). The ABL 330 uses temperature-correction algorithms derived from human hematology to calculate blood bicarbonate (HCO_3) and percentage HbO_2. Core body temperatures were not recorded at the time of blood sampling, consequently the blood gas values were not corrected for individual differences in body temperature. After valid blood gas readings were confirmed, the birds were weighed and euthanized with CO_2 gas, and their hearts were dissected to determine ventricular weights. Blood pH values were converted to H ion concentrations for all statistical comparisons and were reconverted to pH values for data presentation.

Statistical Analyses

Mortality incidences were evaluated using a z-test (Jandel Scientific, 1994). Other body weight, feed consumption, and blood gas parameters were analyzed by a t-test (comparison between two groups), or ANOVA on ranks (comparison of multiple groups) where appropriate, and group means were separated using Tukey's Test (Jandel Scientific, 1994). The meat quality data were subjected to ANOVA using general linear models procedures (SAS Institute, 1999), and treatment means were separated using Duncan's multiple-range test. In all cases, values were considered to differ at $P \leq 0.05$.

[6]Minolta CR-300; Minolta Corp., Ramsey, NJ.
[7]Radiometer America Inc., Westlake, OH.

TABLE 1. Broilers were injected i.v. with saline or cellulose micro-particles and died within 24 h post-injection (Day 18–19 mortality), during the post-injection recovery period at thermoneutral temperatures (Day 20–35; ascitic, non-ascitic, and total mortality), or during the cyclic heat challenge (Day 36 to 57; ascitic, non-ascitic, and total mortality)

	Injection group		
Variable	Saline (n)	Cellulose (n)	P^1
Experiment 1			
Day 18–19 post-injection mortality, %	0 (0/144)	45.5 (135/297)	0.001
Day 20–35 ascites mortality, %	0.7 (1/144)	6.8 (11/162)	0.012
Day 20–35 non-ascitic mortality, %	2.1 (3/144)	11.1 (18/162)	0.004
Day 20–35 total mortality, %	2.8 (4/144)	17.9 (29/162)	0.001
Day 36 to 57 ascites mortality, %	4.0 (5/124)	3.3 (4/122)	0.962
Day 36 to 57 non-ascitic mortality, %	8.9 (11/124)	2.5 (3/122)	0.059
Day 36 to 57 total mortality, %	12.9 (16/124)	5.7 (7/122)	0.085
Experiment 2			
Day 19 post-injection mortality, %	0.5 (1/169)	55.4 (217/392)	0.001
Day 20 to 35 ascites mortality, %	10.1 (17/168)	14.3 (25/175)	0.307
Day 20 to 35 non-ascitic mortality, %	0.6 (1/168)	3.4 (6/175)	0.145
Day 20 to 35 total mortality, %	10.7 (18/168)	17.7 (31/175)	0.089
Day 36 to 57 ascites mortality, %	2.8 (4/140)	1.4 (2/140)	0.689
Day 36 to 57 non-ascitic mortality, %	17.1 (24/140)	11.4 (16/140)	0.233
Day 36 to 57 total mortality, %	20.0 (28/140)	12.9 (18/140)	0.124
Experiments 1 and 2			
Day 19 post-injection mortality, %	0.3 (1/313)	51.1 (352/689)	0.001
Day 20 to 35 ascites mortality, %	5.8 (18/312)	10.7 (36/337)	0.035
Day 20 to 35 non-ascitic mortality, %	1.3 (4/312)	7.1 (24/337)	0.001
Day 20 to 35 total mortality, %	7.1 (22/312)	17.8 (60/337)	0.001
Day 36 to 57 ascites mortality, %	3.4 (9/264)	2.3 (6/262)	0.543
Day 36 to 57 non-ascitic mortality, %	13.3 (35/264)	7.3 (19/262)	0.017
Day 36 to 57 total mortality, %	16.7 (44/264)	9.5 (25/262)	0.009

[1]Mortality incidences were compared between injection groups within a variable using a z-test (P).

RESULTS

Experiments 1 and 2

Mortality data for Experiments 1 and 2 are summarized in Table 1. Only one bird died within 24 h after the saline injection, whereas approximately half of the broilers injected with cellulose micro-particles died within 24 h post-injection. During the post-injection particle clearance interval (Day 20 to 35), ascitic, nonascitic, and total mortalities were higher for the cellulose group than for the saline group in experiment 1 but not in experiment 2. When the data from both experiments were combined, the incidences of d 20 to 35 ascitic, nonascitic, and total mortality were higher in the cellulose group than in the saline group. In contrast, the combined data from both experiments during cyclic heat exposure (d 36 to 57) reflected lower levels of nonascitic and total mortality for the cellulose group when compared with the saline group (Table 1).

Pre-injection body weights were not recorded in Experiment 1. The pre-injection body weights recorded on d 18 and 19 in Experiment 2 averaged 637 ± 4 g for the saline group and 626 ± 3 g for the cellulose group (mean ± SEM; n = 169 for saline, 395 for cellulose; $P < 0.05$). Within the cellulose group, birds that survived for 24 h post-injection were heavier (634 ± 4 g) than those that succumbed (615 ± 4 g) (mean ± SEM; n = 175 survivors, n = 217 that died, $P < 0.05$). As shown in Figure 1, substantial overlap existed in the pre-injection body weight values for cellulose-injected broilers that remained alive or succumbed within 24 h post-injection, providing no compelling rationale for adjusting the micro-particle injection dosage for individual differences in body weight.

The d 36 and final body weights and the d 36 to final body weight gain, feed consumption, and feed:gain ratios for saline-injected broilers and broilers that recovered from injections of cellulose micro-particles are summarized in Tables 2 and 3. The values shown in Table 2 were calculated using body weight data for every broiler included in each group at the beginning of the heat-stress challenge (d 36), including those broilers that subsequently died before d 57. The values shown in Table 3 were calculated using only the body weight data from those broilers remaining alive through d 57. These different computational approaches nevertheless generated similar mean values for each variable, an unanticipated finding attributable to a tendency for birds that died to lose weight prior to death. For example, of the 69 birds in both experiments that were weighed on d 36 and then died before d 57, 45% lost weight prior to death, and the overall weight gain averaged less than 100 g per bird. In contrast, of the 457 saline and cellulose-injected birds in both experiments that survived through d 57, 99% gained weight between d 36 and 57, and the overall weight gain averaged more than 1,200 g per bird.

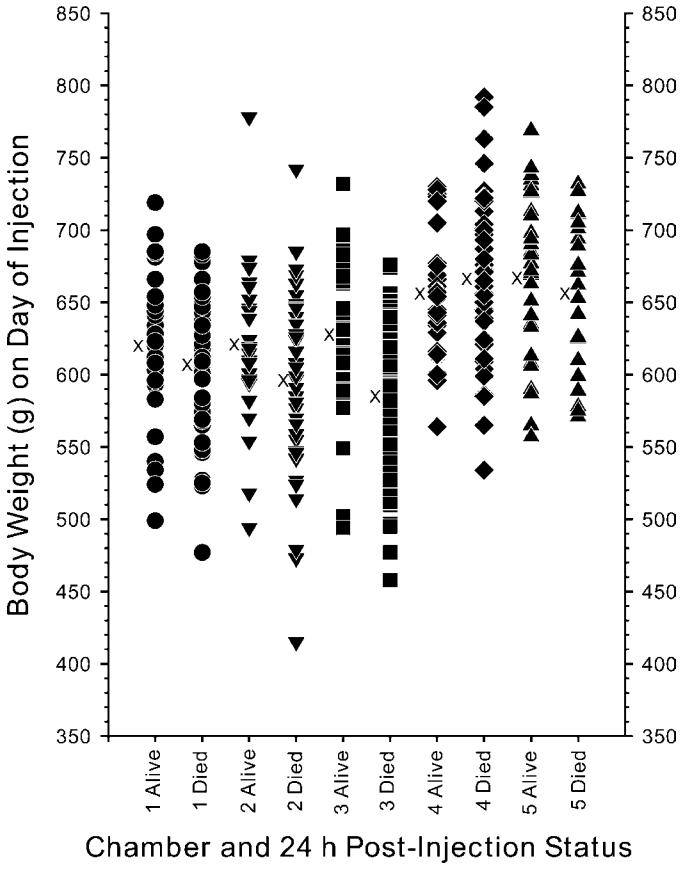

FIGURE 1. Scatter plots of individual body weights for male broilers that were injected i.v. with 0.4 mL of cellulose micro-particles on d 18 (environmental chambers 1, 2, and 3) or d 19 (environmental chambers 4 and 5) and then within 24 h post-injection remained alive (1 Alive, 2 Alive, 3 Alive, 4 Alive, 5 Alive) or died (1 Died, 2 Died, 3 Died, 4 Died, 5 Died). The mean value (X) for each chamber half is shown to the left of each column of individual values.

When compared with the saline group within separate or combined experiments, the survivors of cellulose injections were consistently lighter on d 36 and had greater body weight gains (d 36 to final), but were not heavier on d 57, regardless of the method of computing the body weight data (Tables 2 and 3). No differences were observed between the saline and cellulose groups for feed consumption or feed:gain ratios calculated on a chamber-half basis (Tables 2 and 3). The L* values, drip losses, and cook losses did not differ between the saline and cellulose groups (Tables 4 and 5).

Experiment 3

For the saline-injected broilers, one bird died within 24 h post-injection (1/80 = 1.2%), and one bird developed ascites between d 20 and 35 (1/79 = 1.3%). For broilers injected with cellulose micro-particles, 46% (92/200) died within 24 h post-injection ($P = 0.001$ compared with saline), and 16.7% (18/108) developed ascites between d 20 and 35 ($P = 0.001$ compared with saline). At 47 to 49 d of age, the broilers in the thermoneutral cellulose group were heavier than those in the thermoneutral saline group, and broilers in both thermoneutral groups were heavier than those in the groups exposed to cyclic heat (Table 6). Ventricular weights increased in proportion to body weight, and after normalization for body weight, the relative ventricular weights for the thermoneutral cellulose group remained higher than those of the cyclic heat saline group. The cellulose group from the thermoneutral chambers also had a higher right:total ventricular weight ratio than the saline group from the cyclic heat chambers (Table 6).

Values for pH, $PaCO_2$, and HCO_3 are shown in Figure 2, and values for PaO_2, and HbO_2 are shown in Figure 3. The cellulose and saline groups did not differ from one another at any sampling interval within the thermoneutral regimen or the cyclic heat regimen. During the initial sample collection, all birds in the cyclic heat chambers were panting, whereas none of the birds in the thermoneutral chambers were panting. Within 30 min after shifting the cyclic heat groups to a thermoneutral environment (+30-min samples) all birds had ceased panting, whereas all of the thermoneutral birds shifted to the hot environment began to pant within 30 min. Initially both cyclic heat groups had elevated arterial blood pH values when compared with both thermoneutral groups. During the initial sample, both cyclic heat groups had lower $PaCO_2$ values when compared with the thermoneutral cellulose group.

After the shift in temperature regimens, both of the thermoneutral groups developed higher arterial blood pH and lower $PaCO_2$ values when compared with their initial values, the arterial pH of the thermoneutral saline group increased above the pH of both cyclic heat groups, and changes in HCO_3 were inconsistent (Figure 2). Also following the shift in temperature regimens, the PaO_2 values for both cyclic heat groups increased, and those for both thermoneutral groups decreased when compared with the respective initial values, as well as for comparisons between the +30- and +60-min sampling intervals. When compared with the thermoneutral cellulose group, both cyclic heat groups had higher HbO_2 values at the +30- and +60-min sampling intervals; however, no time-dependent changes in HbO_2 were detected (Figure 3).

DISCUSSION

The unilateral pulmonary artery occlusion and intravenous micro-particle injection techniques were developed to eliminate broilers that are unable to accommodate increases in blood flow through a restrictive pulmonary vasculature. Broilers succumbing to respiratory insufficiency following unilateral pulmonary artery occlusion or micro-particle injections are considered to have marginal cardiopulmonary capacities, whereas the clinically healthy survivors apparently have reserve capacities sufficient to confer genetic resistance to PHS. The dosages of cellulose micro-particles injected in the present study caused 24 h post-injection mortality or ascites in over half of the birds by d 35. The survivors presumably represented the most robust cohort of the population, whereas the broilers injected with saline alone experienced low

TABLE 2. Body weight, body weight gain, feed consumption, and feed:gain ratios for all broilers that were injected i.v. with saline or cellulose micro-particles and were exposed to a cyclic heat challenge beginning on d 36[1]

	Injection group		
Variable	Saline	Cellulose	*P*
Experiment 1			
Individual BW d 36, g	1,989 ± 15	1,906 ± 17	0.001
Individual BW final, g	3,092 ± 49	3,173 ± 37	0.179
Individual BW gain d 36 to final, g	1,102 ± 42	1,267 ± 34	0.003
Feed consumed/chamber d 36 to 57, kg[2]	100.2 ± 3.4	106.5 ± 4.6	0.316
BW gain/chamber d 36 to final, kg	34.1 ± 1.7	38.6 ± 2.4	0.172
Feed:gain/chamber d 36 to 57	2.94 ± 0.07	2.76 ± 0.05	0.800
Experiment 2			
Individual BW d 36, g	2,029 ± 13	1,967 ± 11	0.001
Individual BW final, g	2,915 ± 53	3,066 ± 49	0.036
Individual BW gain d 36 to final, g	886 ± 51	1,099 ± 48	0.002
Feed consumed/chamber d 36 to 57, kg[2]	82.9 ± 4.0	89.8 ± 2.9	0.195
BW gain/chamber d 36 to final, kg	24.8 ± 3.0	30.8 ± 2.7	0.176
Feed:gain/chamber d 36 to 57	3.55 ± 0.42	2.98 ± 0.17	0.242
Experiments 1 and 2			
Individual BW d 36, g	2,010 ± 10	1,939 ± 10	0.001
Individual BW final, g	2,997 ± 37	3,116 ± 31	0.064
Individual BW gain d 36 to final, g	987 ± 34	1,177 ± 30	0.001
Feed consumed/chamber d 36 to 57, kg[2]	90.6 ± 3.9	97.2 ± 3.8	0.244
BW gain/chamber d 36 to final, kg	29.0 ± 2.4	34.3 ± 2.2	0.120
Feed:gain/chamber d 36 to 57	3.28 ± 0.25	2.88 ± 0.10	0.157

[1]Values for each variable represent the mean ± SEM for all broilers included in each group on d 36 including those that subsequently died (see Table 1).

[2]Feed consumed/chamber, BW gain/chamber, and feed:gain values represent the group means ± SE for all broilers in four chambers in experiment 1 and five chambers in experiment 2.

mortality and, therefore, represent the population continuum. As outlined in the Introduction, the possibility exists that rigorous selection for an improved pulmonary vascular capacity might also improve the efficiency of pulmonary gas diffusion or the sensitivity of chemoreceptor-mediated ventilatory control. If so, then the survivors of cellulose micro-particle injections potentially could be more susceptible to respiratory alkalosis induced by acute

TABLE 3. Body weight, body weight gain, feed consumption, and feed:gain ratios for broilers that survived through d 57 following an i.v. injection of saline or cellulose micro-particles and exposure to a cyclic heat challenge[1]

	Injection group		
Variable	Saline	Cellulose	*P*
Experiment 1			
Individual BW d 36, g	2,003 ± 14	1,906 ± 18	0.001
Individual BW d 57, g	3,240 ± 31	3,233 ± 31	0.878
Individual BW gain d 36 to 57, g	1,236 ± 27	1,327 ± 25	0.015
Feed consumed/chamber d 36 to 57, kg[2]	100.2 ± 3.4	106.5 ± 4.6	0.316
BW gain/chamber d 36 to 57, kg	33.4 ± 2.3	38.2 ± 2.5	0.211
Feed:gain/chamber d 36 to 57	3.03 ± 0.12	2.80 ± 0.07	0.168
Experiment 2			
Individual BW d 36, g	2,035 ± 15	1,966 ± 12	0.001
Individual BW d 57, g	3,140 ± 44	3,221 ± 39	0.161
Individual BW gain d 36 to 57, g	1,104 ± 41	1,255 ± 36	0.006
Feed consumed/chamber d 36 to 57, kg[2]	82.9 ± 4.0	89.8 ± 2.9	0.195
BW gain/chamber d 36 to 57, kg	24.7 ± 3.2	30.6 ± 2.7	0.196
Feed:gain/chamber d 36 to 57	3.59 ± 0.47	3.00 ± 0.18	0.270
Experiments 1 and 2			
Individual BW d 36, g	2,020 ± 10	1,937 ± 11	0.001
Individual BW d 57, g	3,189 ± 27	3,228 ± 25	0.486
Individual BW gain d 36 to 57, g	1,169 ± 25	1,291 ± 23	0.001
Feed consumed/chamber d 36 to 57, kg[2]	90.6 ± 3.9	97.2 ± 3.8	0.244
BW gain/chamber d 36 to 57, kg	28.6 ± 2.4	34.0 ± 2.2	0.122
Feed:gain/chamber d 36 to 57	3.34 ± 0.27	2.91 ± 0.11	0.158

[1]Values for each variable represent the mean ± SEM for only those broilers remaining alive in each group through d 57 (see Table 1).

[2]Feed consumed/chamber, BW gain/chamber, and feed:gain values represent the group means ± SE for broilers remaining alive through d 57 in four chambers in experiment 1 and five chambers in experiment 2.

TABLE 4. Muscle pH at different postmortem times for broilers that survived an i.v. injection of saline or cellulose micro-particles and then were exposed to a cyclic heat challenge in experiment 2[1]

Time (h)	Saline (n = 50)	Cellulose (n = 50)
0.25	6.61 ± 0.02	6.60 ± 0.03
1.25	6.51 ± 0.02	6.52 ± 0.02
2.5	6.28 ± 0.03	6.32 ± 0.02
4.0	6.05 ± 0.02	6.06 ± 0.02
6.0	5.76 ± 0.03	5.79 ± 0.03

[1]Values within each group represent the mean ± SEM.

or chronic heat challenges. However, the moderate heat challenge imposed in the present study did not reveal differences in blood gas values between the cellulose and saline groups within a temperature regimen, regardless of whether the broilers were chronically acclimated to heat (cyclic heat regimen) or were exposed to an acute heat challenge at the end of the experiment (thermoneutral regimen).

The results of this study were consistent with previous reports that blood PaO_2 and HbO_2 values remain unchanged or may decrease modestly when non-acclimated poultry undergo acute heat stress. Apparently the lower affinity of hemoglobin for oxygen attributable to an increase in body temperature is effectively counteracted by the higher affinity associated with the concurrent panting-induced decrease in $PaCO_2$ and alkaline blood pH (Pinshow et al., 1985; Isaacks et al., 1986). Consequently, mortality due to heat stress has never been attributed to hypoxemia (low blood oxygen) in poultry (Frankel and Frascella, 1968; Edens and Siegel, 1974; Kohne and Jones, 1975; Arad, 1983; Darre and Harrison, 1987). However, in view of the panting-induced hyperventilation of the gas exchange surfaces, it remains somewhat surprising that slight reductions in PaO_2 can be detected in acutely heat-challenged broilers and that the PaO_2 improved when broilers acclimated to cyclic heat were transferred from 35 to 24°C (Darre and Harrison, 1987; present study, Figure 3). The diffusion rate for O_2 across biological membranes is 30-fold slower than for CO_2, and so the possibility exists that a modest pulmonary diffusion limitation for O_2 (but not CO_2) is exposed in conjunction with heat-induced increases in cardiac output (Wideman and Kirby, 1995; Wideman, 2000, 2001). The magnitude of the cardiac output directly reflects the whole body demand for O_2, and cardiac output increases to supply the additional O_2 needed to maintain a constant core body temperature when the environmental temperature is outside of the thermoneutral zone (Whittow et al., 1964; Darre and Harrison, 1987; Wideman, 1999).

The thermoneutral zone is defined as the range of air temperatures at which the basal metabolic rate, O_2 uptake, and heat production remain essentially low and constant. At temperatures below the thermoneutral zone, O_2 consumption and heat production increase to prevent the core body temperature from dropping, and at temperatures above the thermoneutral zone, O_2 consumption again increases to support the additional work performed by skeletal muscle (panting) and cardiac muscle (increased blood flow to the periphery) to dissipate body heat (King and Farner, 1961; Smith and Oliver, 1971; Whittow, 1976; Darre and Harrison, 1979; Yahav et al., 1995). Domestic fowl that survive initial exposures to high environmental temperatures become acclimated and subsequently are capable of reducing their oxygen consumption and cardiac output during high temperature challenges (Vogel and Sturkie, 1963; Weiss et al., 1963; Sturkie, 1970; Yahav, 2000). If confirmed by future studies, a direct association between increases in cardiac output and modest reductions in PaO_2 in heat-stressed broilers would further implicate inadequate pulmonary vascular capacity and mild hypoxemia as factors that potentially may limit broiler performance during acute exposure to high environmental temperatures.

Ascitic, nonascitic, and total mortalities during the post-injection particle clearance interval from d 20 to 35 were higher for the cellulose group than for the saline group in experiment 1 but not in experiment 2. The lower micro-particle injection doses used in experiment 2 (0.40 mL) when compared with experiment 1 (0.45 mL) did not alter the 24 h post-injection mortality or the total mortality values from d 20 to 35 for the two experiments, consequently it was the inexplicably higher d 20 to 35 ascites mortality evident in the saline-injected controls that reduced the group differences in experiment 2. Pre-

TABLE 5. Comparison of lightness (L*) values, drip loss and cook loss for broilers that survived an i.v. injection of saline or cellulose micro-particles and then were exposed to a cyclic heat challenge in experiment 2[1]

Variable	Saline (n = 50)	Cellulose (n = 50)
L* value (4 h)	49.23 ± 0.28	49.97 ± 0.33
L* value (24 h)	52.72 ± 0.29	53.25 ± 0.35
Drip loss (%)	0.57 ± 0.06	0.84 ± 0.11
Cook loss (%)	14.58 ± 0.53	14.52 ± 0.46

[1]Values within each group represent the mean ± SEM.

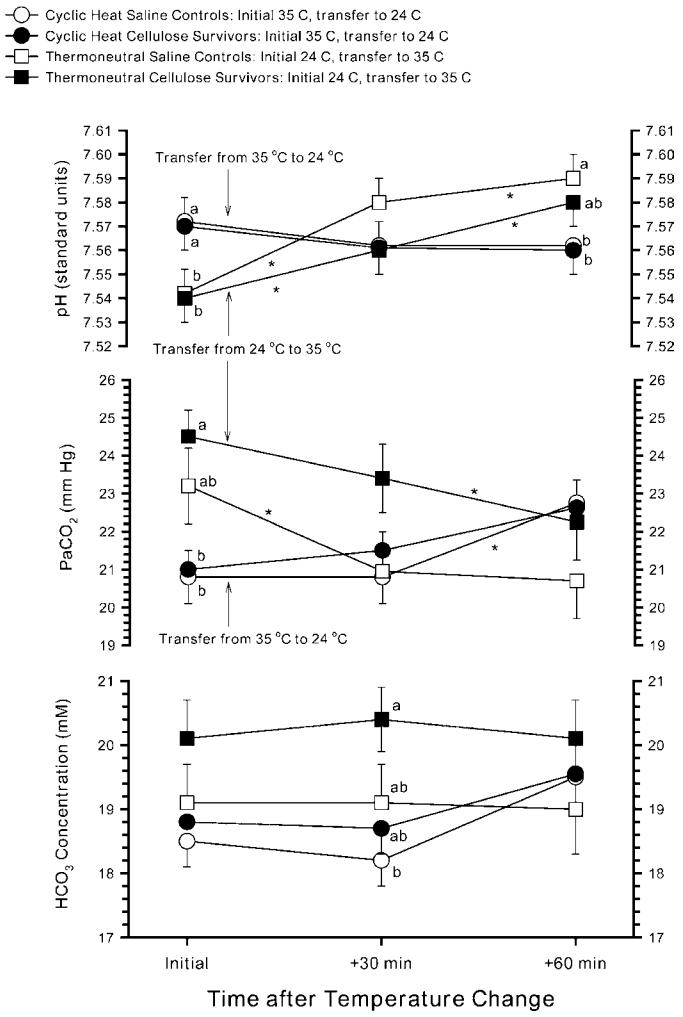

FIGURE 2. The arterial blood pH, partial pressure of CO_2 ($PaCO_2$), and bicarbonate (HCO_3) concentration for 47- to 49-d-old male broilers reared under cyclic heat (35°C: circles; mean ± SEM, n = 15 per group) or thermoneutral (24°C: squares; mean ± SEM, n = 15 per group) temperature regimens, during an initial interval when they remained exposed to their original temperature regimen (Initial), and at 30 and 60 min after the cyclic heat groups had been transferred to 24°C, or the thermoneutral groups had been transferred to 35°C (+30 min, +60 min). The saline control (open symbols) and cellulose survivor (closed symbols) groups had been injected with heparinized saline alone or cellulose micro-particles suspended in heparinized saline at 18 to 19 d of age, respectively. Different letters (a,b) designate differences ($P \leq 0.05$) between the groups within a sample interval. Asterisks (*) denote values within a group that changed when compared with the Initial sample interval.

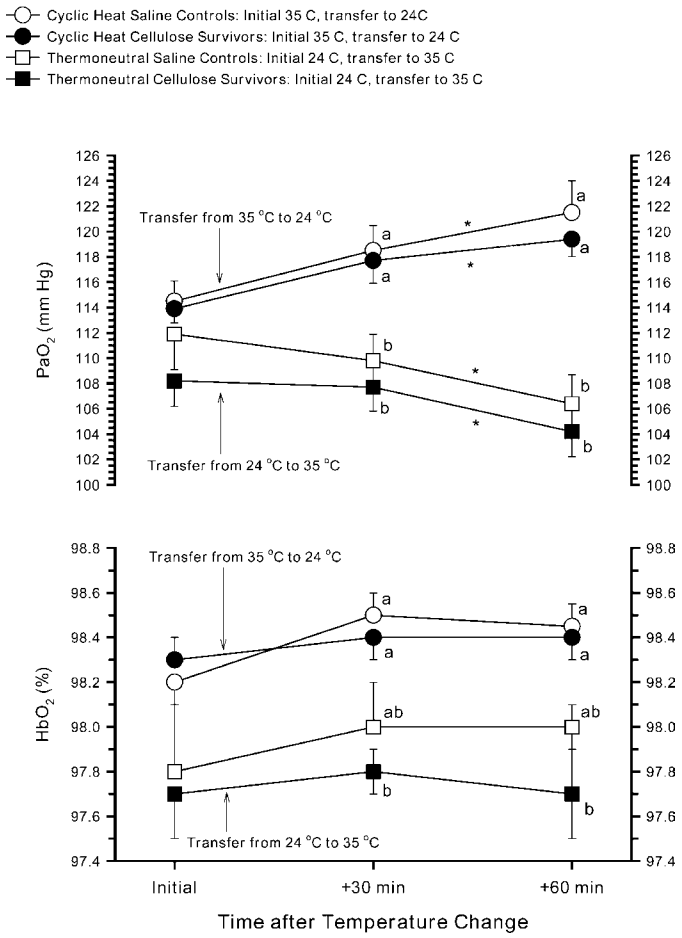

FIGURE 3. The arterial blood partial pressure of O_2 (PaO_2) and saturation of hemoglobin with O_2 (HbO_2) for 47- to 49-d-old male broilers reared under cyclic heat (35°C: circles; mean ± SEM, n = 15 per group) or thermoneutral (24°C: squares; mean ± SEM, n = 15 per group) temperature regimens, during an initial interval when they remained exposed to their original temperature regimen (Initial), and at 30 and 60 min after the cyclic heat groups had been transferred to 24°C, or the thermoneutral groups had been transferred to 35°C (+30 min, +60 min). The saline control (open symbols) and cellulose survivor (closed symbols) groups had been injected with heparinized saline alone or cellulose micro-particles suspended in heparinized saline at 18 to 19 d of age, respectively. Different letters (a,b) designate differences ($P \leq 0.05$) between the groups within a sample interval. Asterisks (*) denote values within a group that changed when compared with the Initial sample interval.

viously, we emphasized that the post-injection mortality and ascites incidence following micro-particle injections can be influenced by the preexisting environmental conditions, cardiopulmonary status, and respiratory health of the broilers being evaluated (Wideman et al., 2002). Preexisting conditions affecting the d 20 to 35 mortality might have interacted with the slightly more rigorous heat challenge in experiment 2 (37°C peak temperature) to generate higher total mortalities at d 36 to 57 and slower growth in the saline and cellulose groups when compared with experiment 1 (35°C peak temperature). The combined data for d 36 to 57 from both experiments indicated that the survivors of the cellulose micro-particle injections generally had lower overall nonascitic and total mortalities and gained more body weight than the saline-injected controls during the cyclic heat challenge. These observations raise the tentative possibility that selection strategies focused on enhancing the cardiopulmonary capacity to accommodate increases in cardiac output may contribute to improved growth and livability when broilers are exposed to moderate heat stress. Indeed, evaluation of the interactions between the environment and the growth potential of broiler lines suggested that susceptibility to ascites during cool temperature exposure may be genetically linked with susceptibility to growth suppression during heat stress (Deeb et al., 2002). However, any advantages conferred by such selection for cardiopulmonary capacity may be overwhelmed by the sequelae to more extreme heat stress or respiratory challenges.

TABLE 6. Body weight, ventricle weight, and ventricular weight ratios for male broilers evaluated at 47 to 49 d of age that had survived i.v. injections of saline or cellulose micro-particles at 20 d of age and were reared under constant thermoneutral (24°C) temperatures or exposed to a cyclic heat challenge (24 to 35°C) beginning at 35 d of age[1]

	Rearing temperature			
	Cyclic heat		Thermoneutral	
Variable	Saline	Cellulose	Saline	Cellulose
Body weight (g)	2,655 ± 50[c]	2,668 ± 38[c]	2,935 ± 72[b]	3,221 ± 43[a]
Right ventricle (g)	1.82 ± 0.08[c]	2.12 ± 0.13[bc]	2.38 ± 0.15[b]	2.98 ± 0.16[a]
Right ventricle/BW	0.0007 ± 0.0001[b]	0.0008 ± 0.0001[ab]	0.0008 ± 0.0001[ab]	0.0009 ± 0.0001[a]
Total ventricle (g)	8.33 ± 0.23[c]	8.76 ± 0.33[c]	10.04 ± 0.34[b]	11.83 ± 0.30[a]
Total ventricle/BW	0.0031 ± 0.0001[b]	0.0033 ± 0.0001[b]	0.0034 ± 0.0009[ab]	0.0037 ± 0.0001[a]
Right:total ventricle	0.22 ± 0.01[b]	0.24 ± 0.01[ab]	0.24 ± 0.01[ab]	0.25 ± 0.01[a]

[a–c]Means ± SEM (n = 15 per group) within each variable with no common superscript differ significantly ($P \leq 0.05$).

Alternative interpretations of the experimental results cannot comfortably be discounted based on the evidence available. For example, previous studies revealed a slight tendency toward lower body weights for broilers that survive cellulose micro-particle injections (Wideman et al., 2002), lending support to the possibility that a lower body weight at the time of micro-particle injection may improve survivability if the cardiac output also is lower (Wideman, 1999) and if there is a proportional improvement in the lung capacity:body weight ratio (Julian, 1989; Owen et al., 1995). The substantial overlap of body weight distributions for broilers that survived vs. those that succumbed to cellulose micro-particle injections failed to support a need to adjust the dosage of injected micro-particles based on individual size differences at the time of injection (Wideman et al., 2002; present study), and the extensive overlap contradicts the possibility that broilers having a slow early growth curve constitute the majority of the micro-particle injection survivors (Figure 1). Nevertheless, broilers injected with cellulose micro-particles do undergo a substantial post-injection depression and hypoxemic stress that definitely could contribute to lower body weights in the survivors when compared on d 36 with the saline group. This early stress conditioning coupled with a lower body weight at the onset of the heat challenge might have contributed to improved thermal tolerance and provided an opportunity for compensatory growth (Deaton et al., 1973; Edens and Siegel, 1974; Arjona et al., 1988; Yahav and Hurwitz, 1996; Yahav, 2000; Yahav and McMurtry, 2001).

To the extent that ventricular weights reflect cardiac work performed to propel the cardiac output through the pulmonary (right ventricle) or systemic (left ventricle) vascular beds (Wideman, 2001), the differences in absolute ventricular weights between temperature regimens in experiment 3 appear to primarily reflect the anticipated reduction in body weight for the 47-to-49-d-old broilers subjected to a chronic heat challenge when compared with flock mates reared at thermoneutral temperatures (Meltzer, 1983; Yahav et al., 1995, 1996). The absence of differences in ventricular weights normalized for body weight, or in right to total ventricular weight ratio, between the saline and cellulose groups within a temperature regimen in experiment 3 is consistent with previous observations and provides further support that there is little evidence of sustained pulmonary hypertension attributable to the microvascular obstruction initiated on d 20 by i.v. cellulose injections (Wideman and Erf, 2002; Wideman et al., 2002). Meat quality characteristics did not differ between the saline and cellulose groups in experiment 2, providing no evidence of differential responses related to the antemortem or postmortem effects of hyperthermia on muscle cell membrane integrity or metabolism (Mitchell et al., 1999; Sandercock et al., 2001).

Overall, none of the observations in the present study provided evidence of detrimental consequences when the cellulose injection survivors were exposed to moderate chronic or acute heat challenges. The cellulose survivors did not differ in susceptibility to heat-induced respiratory alkalosis or hypoxemia when compared with their saline-injected flock mates, nor did meat quality characteristics differ between the experimental groups. The combined data from experiments 1 and 2 can be cautiously interpreted to indicate that the survivors of micro-particle injections exhibited improved d 36 to 57 livability and growth without adversely affecting meat quality when compared with their saline-injected flock mates during a moderate heat challenge. The physiological mechanisms involved remain to be defined, nevertheless these results are consistent with the hypothesis that broiler survivors of cellulose micro-particle injections represent a robust cohort of the population that, subsequent to the restoration of pulmonary vascular patency, have the potential to exhibit the anticipated advantages of a superior cardiopulmonary capacity without exhibiting the potentially detrimental influences of respiratory alkalosis or chemoreceptor restraint on evaporative cooling.

ACKNOWLEDGMENTS

This research was supported by Hubbard ISA, Hot Springs, AR.

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