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Chapter 13

Ascites Syndrome in Broiler Chickens – A Physiological Syndrome Affected by Red Blood Cells

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Additional information is available at the end of the chapter

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1. Introduction

Reduced oxygen availability to the tissues (hypoxia) poses numerous challenges to animal life. Hypoxia occurs as a result of diminished partial pressure of oxygen, such as occurs with increasing altitude, or reduced oxygen percentage in the air capillaries of the lung. The oxygen partial pressure drops by approximately 7 mm Hg, i.e, approximately 2.5% in the case of atmospheric oxygen, for each 1,000 m increase in altitude, and thereby reduces the amount of oxygen available to the hemoglobin in red blood cells as blood passes through the lung.

The hypoxia tolerance of birds has been suggested to be greater than that of mammals. Early studies found that lowland house sparrows (*Passer domesticus*) in a wind tunnel at a simulated altitude of 6100 m behaved normally and flew for short periods [1]. Such findings support the anatomical and physiological evidence that the O_2 transport pathway of birds has several unique characteristics that help support energetic activity and aerobic metabolism during hypoxia.

The O_2 cascade from inspired air to the tissue mitochondria includes several convective and diffusive steps at which physiological adjustments can preserve the rate of O_2 flux in spite of hypoxia, thereby ensuring an uninterrupted supply of O_2 to the energy-producing machinery of the cells [2]. These steps include ventilatory convection, diffusion across the blood–gas interface, circulatory convection, diffusion across the blood–tissue interface (including myoglobin-facilitated diffusion), and O_2 utilization by the tissue mitochondria.

Breathing (ventilation) is stimulated when a decline in arterial PO_2 is sensed by chemoreceptors in the carotid bodies. However, this hypoxic ventilatory response increases respiratory CO_2 loss, causing a secondary hypocapnia (low partial pressure of CO_2 in the

blood) and alkalosis (high pH) in the blood [3]. Hypocapnia reflexively inhibits breathing and causes an acid–base disturbance. It has been suggested that birds have a higher tolerance of hypocapnia than mammals [4], possibly because of an ability to rapidly restore blood pH in the face of CO_2 challenges [5]. The significance of this tolerance is that it would enable birds to ventilate more deeply before depletion of CO_2 in the blood impairs normal function, and thereby to enhance O_2 transport to the gas-exchange surface. It seems that every step in the O_2 transport pathway can be influential, and that the relative benefit of each step changes with the level of O_2 availability.

The acclimatization response to hypoxia generally involves increases in hematocrit (Hct) and in hemoglobin (Hb) concentration, but this adaptive erythropoietic response is complicated [6-9]. It is reasonable to expect that an increased Hct could confer a physiological advantage under hypoxia, by enhancing O_2-carrying capacity, but experimental results do not support this [10,11]. A moderately increased Hct enhances arterial O_2 content and therefore increases aerobic capacity [12-14], but the highest attainable Hct is not necessarily associated with the highest possible aerobic power output [15,16]. This is because the associated increase in blood viscosity increases the peripheral vascular resistance, and this might compromise cardiac output (Q), thereby reducing the O_2 consumption rate ($\dot{V}O_2$) [17,18].

Another mechanism that can sustain/enhance O_2 transport under hypoxia is alteration in the O_2-binding properties of Hb in the blood. These alterations could be mediated by changes in the intrinsic Hb–O_2 affinity, changes in the sensitivity of Hb to allosteric cofactors that modulate Hb–O_2 affinity, and/or changes in the concentration of allosteric cofactors within the erythrocytes [19-22].

Numerous high-altitude birds, such as the bar-headed goose, the Andean goose [23], and the Tibetan chicken (*Gallus gallus*) [24], possess Hb with an increased O_2 affinity. This can dramatically increase O_2 delivery and pulmonary O_2 loading in hypoxia by increasing the saturation of Hb and, consequently, the O_2 content of the blood at a given O_2 partial pressure. Thus it can greatly improve the O_2 transport pathway [25].

Contrary to the hematological changes that are typically associated with the acclimatization response to hypoxia, genetically based changes in Hb structure that increase intrinsic O_2 affinity or that suppress sensitivity to allosteric cofactors are more important to hypoxia tolerance in naturally high-altitude birds [21,22,26], because in lowland birds an increased Hb–O_2 affinity may hinder O_2 unloading in the tissue capillaries.

Although these distinctive characteristics of birds should enhance hypoxia tolerance by improving the overall capacity for O_2 transport, being avian is not in itself sufficient for coping with hypoxia. Domesticated meat-type chickens (broilers) exhibit high O_2 requirements because of their very fast growth and, consequently, they may have a reduced blood O_2 level, i.e., hypoxemia [27-31] resulting from vigorous digestion and metabolism which have high O_2 requirements. When O_2 demand increases, heart rate and cardiac output increase, thereby increasing the flow of blood through the lung and the pressure required to force blood through the arterioles and capillaries of the lung. The increased flow rate and

increased transit time may not allow the red blood cells to pick up a full load of O_2, so that hemoglobin O_2 saturation is not complete, which causes hypoxemia [32].

Hypoxia/hypoxemia directly stimulates the endothelial and smooth muscle cells in pulmonary blood vessels, causing vasoconstriction throughout the lungs and an increase in pulmonary blood pressure that can persist for a long time at high altitude [33,34]. This global vasoconstriction impairs O_2 diffusion because it can divert blood flow away from the gas-exchange surface to pulmonary shunt vessels [35], and the resultant pulmonary hypertension can cause fluid leakage into the air spaces, which, in turn, causes a thickening of the O_2 diffusion barrier [36,37]. Hypoxic pulmonary hypertension can also overburden the right ventricle of the heart and can contribute to pathophysiological conditions, such as chronic mountain sickness or ascites in broilers [9,38].

Ascites in fast-growing broilers:

The commercial broiler of today represents the culmination of dramatic changes over the past 60 years. These changes were caused by genetic selection processes that focused mainly on production traits [39,40]; it has been reported that 85-90% of the changes in commercial broilers were directly related to genetic aspects [39-42]. Commercial broilers of 1991 were compared with the Athens-Canadian Random Bred Control Population, which represents the commercial broilers of 1957 [39,40]. Average daily weight gain of the 1957 and 1991 broilers were 10 and 31 g/d, respectively, from hatch to 3 weeks of age, and 19 and 68 g/d, respectively, from 3 to 6 weeks. The higher growth rate (GR) is driven by a higher feed intake per unit time and higher metabolic rate and, consequently, a higher demand for O_2, from the embryonic stage onward [43-45]. However, it appears that the increase in growth rate occurred without concomitant development in the efficiency of the cardiovascular and the respiratory systems [41,46].

Thus, the increase in metabolic rate, coupled with exposure to environmental conditions such as temperature, lighting and ventilation, and nutritional factors such as feed form or content, all seem to promote the development of ascites [47]. The primary cause of the ascites syndrome, however, is believed to be hypoxia/hypoxemia [48,49], when the bird's demand for O_2 exceeds its cardiopulmonary capacity and causes pulmonary hypertension [50], which results in development of the ascites syndrome (AS) [51-53].

The etiology of the syndrome was well documented previously [52,54,55], and is characterized phenotypically by increased pulmonary hypertension, right-ventricle hypertrophy, fluid accumulation in the pericardium and abdominal cavity, increased hematocrit that results from increased red blood cell production (erythropoiesis), and a decline in arterial blood O_2 saturation [41,52,56,57].

An international survey in commercial broiler flocks showed that AS affected 4.7% of broilers worldwide [58]. Likewise, it was found that over 25% of overall broiler loss in the United Kingdom was a result of AS [59]. It is, therefore, apparent that this syndrome is a serious economic concern in the broiler industry. As the syndrome appears mainly at ages greater than 4 weeks, even 1% of mortality from AS causes significant economic losses,

because it occurs toward the end of the growing period [58] and, therefore, affects heavy birds which have absorbed a considerable investment of labor and feed [60,61]. Two management approaches have been applied in order to minimize the actual AS mortality in commercial flocks: (1) increasing the broiler house temperature by means of heating and insulation, which are costly; and (2) reducing the actual growth rate and, therefore, the metabolic rate and demand for oxygen, by providing fewer hours of light so as to reduce the quantity of feed consumed, and using low-energy mash feeds to reduce intake of dietary energy [47,62]. Thus, while the genetic potential for rapid growth of commercial broilers has been continuously improved by breeding companies [41], its full expression is not allowed at the farm level, specifically to avoid morbidity and mortality of AS-susceptible birds. Consequently production costs are increased because of the longer period of rearing to marketing body weight.

There are two alternative hypotheses regarding the association between GR of contemporary broilers and their susceptibility or resistance to AS. Many studies showed that AS does not develop in slow-growing chickens, egg-type Leghorns [see, e.g., 63,64], or slow-growing broilers [see, e.g., 65,66]. It has been suggested that high GR is the direct cause of AS, because of the consequent high demand for oxygen by tissues and organs of these birds. According to this hypothesis, alleles or genotypes that increase GR of broilers also increase their tendency to develop AS. Such a situation should be manifested in a symmetrical genetic correlation between GR and AS: genetic differences in GR – whether between lines or families, or between individuals within lines – should be associated with corresponding differences in %AS. Symmetrically, individuals that develop AS, or families with higher %AS, should have a genetic potential for a higher GR than their counterparts that remain healthy under the same rearing conditions.

The second hypothesis asserts that broilers do not have to be the fastest growing birds in a flock in order to develop AS, but simply need to have their weight-gain rate exceed the growth rate of their pulmonary vascular capacity [67-71]. According to this hypothesis, there should be high-GR broilers that do not develop AS despite their high O_2 demand, because they are genetically resistant. Similarly, there should be broilers with genetically low GR that, nevertheless, are susceptible to AS, although they require special environmental conditions to express this susceptibility.

The hypotheses regarding an inherent association between AS and the genetic potential for high GR were tested by examining contemporary commercial broilers in 2002 and 2006, and an experimental low-GR slow-growing line [71]. All the lines were tested under the same experimental protocol, that allowed measurement of GR under standard brooding conditions (SBCs) up to d 19, and then efficiently distinguished between AS-susceptible and AS-resistant individuals, the latter being those that remained healthy under the same high-challenge, ascites-inducing conditions (AICs) – conditions based on exposure to low ambient temperatures while receiving different forms of diet [72]. Ascites syndrome incidence was 31 and 47% in the 2002 and 2006 birds respectively, and 32% in the 1986 slow-growing line (Table 1). Most broilers that remained healthy under the high-challenge AICs exhibited the same early GR and BW as those that later developed AS. These results, and the

approach has not been used by breeding companies, because it would force them to compromise the selection for more important traits, such as growth rate and meat yield, which are not fully expressed under AIC.

Indirect selection against susceptibility to AS, cardiovascular indicators:

Many studies focused on identifying reliable diagnostic indicators for AS in broilers. Hematocrit (HCT) is a marker for high rate of erythropoiesis in ascitic birds, therefore it is always significantly higher in AS broilers than in their healthy counterparts reared under the same conditions [30,54,60,115,124,125,139,154]. HCT values from broilers aged 35 and 44 d were used to screen one sire line and two dam lines for AS susceptibility [154]: they were used to select individuals that were considered the most (> 36%) and least (< 29%) AS susceptible, and the males and females with the highest and lowest HCT values, from the two dam lines, were selected and classified as high hematocrit (H) and low hematocrit (L) groups. These individuals were then reared under broiler breeder management conditions. Males and females within each group were mated, to create offspring that were HH, HM-no definition for HM, LM, and LL. The progeny underwent screening for hematocrit on days 6, 42, and 49, and from d 33 onward birds were subjected to cold stress. Differences in HCT values were seen at d 6: the HH chicks had significantly higher values than all other groups. On d 49 HCT values of the HH birds were significantly higher than those of the LL birds. Cold stress increased AS mortality in all combinations, but the HH birds had significantly higher AS mortality then the LL birds, which suggests that HCT value is heritable. It was also suggested that HCT screening and selection based on HCT values could be effective in developing resistant populations of broilers. However, later studies revealed that the variation in HCT was a secondary manifestation of developing AS, therefore it could not be used as an early indicator of AS sensitivity under normal conditions [57,72]. Heart rate (HR), measured by pulse oximetry or by encephalography, was found to be lower in broilers suffering from AS than in healthy ones [111,163,185]. At 35 days of age, HR in feed-restricted broilers was significantly higher than that in fast-growing broilers, and the HR of broilers suffering from congestive heart failure, which is associated with hypoxemia and AS, was significantly lower than that of feed-restricted, slow-growing broilers and healthy fast-growing broilers [64]. Broilers with AS were found to have a significantly lower SaO_2 than their healthy counterparts at the age of 6 weeks (62.1 and 86.0%, respectively) [30]. Broilers with AS induced by a pulmonary artery clamp had a significantly lower SaO_2 and higher right-ventricle:total-ventricle weight ratio (hypertrophy of the right ventricle RV:TV) than those of healthy, non-AS broilers [32]. Therefore, low SaO_2 was suggested to be a reliable genetic early indicator for AS susceptibility [186]. In recent years, some breeding companies have selected against broilers with low SaO2, as measured in selection candidates at 5 wk of age [187]. However, because of the low %AS in these unstressed flocks, high SaO_2 levels are expected in susceptible individuals that do not develop AS; also, low heritability (0.15) was reported for SaO_2 at 5 wk of age in commercial breeding lines [187]. Because of this low heritability and only moderate genetic correlation with actual manifestation of AS, the effectiveness of 5-wk SaO_2 as an indicator for selection against AS susceptibility must be limited. All the cited findings suggest that there is a genetic component for AS mortality and

also for several parameters (e.g., RV:TV and HCT) that have been found to be associated with development of AS; however, the exact biochemical and physiological precursor factors related to the genetic propensity to develop AS are still not known. It is often difficult to determine whether a particular change is primary in nature, and therefore determinative, or is a subsequent secondary manifestation in the development of AS. If parameters to specifically predict AS susceptibility or resistance are sought, it is of paramount importance that the primary changes be determined and evaluated. Moreover, in order to assess their significance as criteria for selection, it is necessary to estimate the heritability of these parameters, and their genetic correlation with consequent AS development under AIC.

In order to conduct advanced physiological and genomic research on AS, and to find the primary cause of AS, identification of all AS-susceptible individuals is crucial. This identification depends solely on mortality or morbidity under AIC. Under low- or medium-challenge AIC, relatively slow-growing broilers or those that can better withstand cold stress, have a relatively lower demand for oxygen and, therefore, do not develop AS. Incorrect identification of AS-susceptible chicks as AS-resistant leads to biased findings regarding the true genetic association between the measured traits and the genetic difference in broilers' susceptibility to AS.

To effectively select against AS susceptibility without interfering with the normal expression of other selected traits, one has to identify the genes responsible for the primary cause of AS or measure their phenotypic expression. There is evidence that the primary cause of AS is manifested in the prenatal or very early postnatal phases, when the cardiovascular system is being developed and is starting to function [188-190]. Measurements of such a manifestation, especially at the embryonic stage, necessitate sacrificing the investigated individuals, rendering it impossible to later determine, under AIC, if these individuals were susceptible or resistant to AS. Therefore, to conduct advanced physiological and genomic research on AS, one needs a pair of selected lines in which all the individuals are either AS-S or AS-R. Comparisons of tissues or functions of individuals from the divergent lines can help to identify the primary cause of AS and thereby to provide an effective indicator for selection against susceptibility. Resource populations derived from crosses between such divergent lines might facilitate genomic research aimed at identifying the genes involved in susceptibility or resistance to AS.

Direct selection against susceptibility to AS

Successful selection against AS susceptibility was conducted in a fully pedigreed elite commercial broiler breeder line [68,184]. Only males and females that did not develop AS following AS-inducing surgery, i.e., unilateral pulmonary artery occlusion, were used for reproduction. After two cycles of such selection, %AS among males that were exposed to low temperatures (14ºC) from 17 to 49 d of age was reduced to 4%, from 31% in the base population and 15% after one cycle. That study demonstrated the feasibility of selection based on mortality of AS-susceptible individuals under a protocol of high-challenge AIC. Divergent selection for AS mortality was conducted by Anthony et al. [78]: the AS was

induced in a hypobaric chamber where oxygen content was reduced to the level equivalent to 2,900 m above sea level. After 10 generations of divergent sire-family selection, %AS increased to about 90% in the AS-susceptible line and decreased to about 20% in the AS-resistant line, thus reaching a divergence of about 70% [78]. Similarly successful divergent selection was applied by Druyan et al. [70]: the 1st selection cycle was based on progeny testing for AS mortality under low-challenge AIC, and two further cycles of full-pedigree progeny testing were conducted under a high-challenge AIC protocol [70,72]. Two divergent lines were established: AS-susceptible (AS-S) and AS-resistant (AS-R), with, respectively, 95 and 5% AS incidence, i.e., a divergence of 90%, when reared together under the same high-challenge AIC [70].

Genomic selection against susceptibility to AS

The very rapid genetic divergence between the selected lines, along with pedigree analysis of %ASF within the AS-S- and AS-R-selected lines implies that a single or a few major genes were responsible for the difference in %AS between the lines [70]. It was concluded that one or more genes was/were involved in the response to a two-cycle selection against AS susceptibility [68]. Single-gene inheritance was also suggested after a complex segregation analysis of data on oxygen saturation of the hemoglobin in arterial blood (SaO_2) [188], a trait known to be closely related to the AS [30,72]. Data on SaO_2 from 12,000 males in fully pedigreed populations of a male line that had been closed for 30 to 40 generations were available for that study. The results suggested that a single diallelic dominant locus was responsible for 90% of the genetic variation in SaO_2, with high levels of SaO_2 indicating AS resistance and low levels indicating AS susceptibility. Data from test-crosses between fully divergent AS-S and AS-R lines suggested a model of complementary interaction between the dominant alleles of two unlinked major genes [77].

If, indeed, only a few genes are involved in genetic control of susceptibility to AS, and in light of the current rapid development and application of genomic tools, the AS genes seem likely to be detected and mapped in the near future. Once mapped, with the help of current and future genomic methodologies, the causative SNPs (or closely linked ones, used as markers) in these genes will be identified. High-throughput genomic assays may soon facilitate efficient genotyping of these marker SNPs, and their routine utilization in commercial breeding programs. With availability of such markers, high-challenge AIC will not be needed to effectively select against susceptibility to AS, because breeders will be able to easily detect and cull individual birds, within the elite lines, that carry the alleles for AS susceptibility. All major broiler-breeding companies have been heavily involved in R&D efforts aimed at achieving this goal.

5. Overall conclusions

Broilers, being highly productive birds, have difficulties in maintaining a dynamic steady-state balance between higher metabolic rate, on the one hand, and, on the other hand, the consequently higher demand for O_2 – a demand that might exceed the cardiovascular

system's capacity to satisfy the O_2 needs. This non-steady-state situation leads to the development of the physiological syndrome – ascites.

Following exposure to AIC of birds from various backgrounds, birds that manifested AS were found to differ significantly from their healthy counterparts, in traits that were measured after initiation of the various AIC protocols, e.g., RV:TV ratio, hematocrit, erythrocyte counts, SaO_2, heart rate, weight gain (WG). These differences are consistent with findings of numerous reports; they represent changes in secondary manifestations of AS and, therefore, could be useful in diagnosis of birds that are developing AS, but not in prediction of AS susceptibility.

Only Druyan's lines that were divergently selected for AS were found to differ significantly in heart rate during the first week of life, when reared under standard brooding conditions (SBCs). Heart rate was significantly higher in the AS-S line than the AS-R line, but before the manifestation of the syndrome no such differences were found between the sick and healthy birds from commercial flocks that were kept under SBCs. Therefore, it appears that higher heart rate cannot be used as a general indicator to identify AS-susceptible broiler chicks.

It is expected that the problem of AS will be solved by genetic eradication of the alleles for AS susceptibility. However, manifestation of AS by genetically susceptible individuals depends on environmental conditions as well as genetic variation in growth rate. Therefore genomic information is required for effective integration of selection against AS susceptibility into breeding programs of commercial broiler stocks.

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