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# 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<sub>2</sub> transport pathway of birds has several unique characteristics that help support energetic activity and aerobic metabolism during hypoxia.

The O<sub>2</sub> cascade from inspired air to the tissue mitochondria includes several convective and diffusive steps at which physiological adjustments can preserve the rate of O<sub>2</sub> flux in spite of hypoxia, thereby ensuring an uninterrupted supply of O<sub>2</sub> 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<sub>2</sub> utilization by the tissue mitochondria.

Breathing (ventilation) is stimulated when a decline in arterial PO<sub>2</sub> is sensed by chemoreceptors in the carotid bodies. However, this hypoxic ventilatory response increases respiratory CO<sub>2</sub> loss, causing a secondary hypocapnia (low partial pressure of CO<sub>2</sub> 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<sub>2</sub> challenges [5]. The significance of this tolerance is that it would enable birds to ventilate more deeply before depletion of CO<sub>2</sub> in the blood impairs normal function, and thereby to enhance O<sub>2</sub> transport to the gas-exchange surface. It seems that every step in the O<sub>2</sub> transport pathway can be influential, and that the relative benefit of each step changes with the level of O<sub>2</sub> 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<sub>2</sub>-carrying capacity, but experimental results do not support this [10,11]. A moderately increased Hct enhances arterial O<sub>2</sub> 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<sub>2</sub> consumption rate (VO<sub>2</sub>) [17,18].

Another mechanism that can sustain/enhance O<sub>2</sub> transport under hypoxia is alteration in the O<sub>2</sub>-binding properties of Hb in the blood. These alterations could be mediated by changes in the intrinsic Hb–O<sub>2</sub> affinity, changes in the sensitivity of Hb to allosteric cofactors that modulate Hb–O<sub>2</sub> 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<sub>2</sub> affinity. This can dramatically increase O<sub>2</sub> delivery and pulmonary O<sub>2</sub> loading in hypoxia by increasing the saturation of Hb and, consequently, the O<sub>2</sub> content of the blood at a given O<sub>2</sub> partial pressure. Thus it can greatly improve the O<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> affinity may hinder O<sub>2</sub> unloading in the tissue capillaries.

Although these distinctive characteristics of birds should enhance hypoxia tolerance by improving the overall capacity for O<sub>2</sub> transport, being avian is not in itself sufficient for coping with hypoxia. Domesticated meat-type chickens (broilers) exhibit high O<sub>2</sub> requirements because of their very fast growth and, consequently, they may have a reduced blood O<sub>2</sub> level, i.e., hypoxemia [27-31] resulting from vigorous digestion and metabolism which have high O<sub>2</sub> requirements. When O<sub>2</sub> 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<sub>2</sub>, so that hemoglobin O<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>, 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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

relatively high incidence of AS in the slow-growing line, indicated that there is very little, if any, direct genetic association between AS and genetic differences in potential GR, which suggests that AS-resistant broilers can be selected for higher GR and remain healthy, even under AICs

| Age (d)                         | 2002 experiment         |                   |                         |                   | 2006 experiment         |                   |                         |                   |
|---------------------------------|-------------------------|-------------------|-------------------------|-------------------|-------------------------|-------------------|-------------------------|-------------------|
|                                 | 1986 broiler line       |                   | 2002 broiler line       |                   | 1986 broiler line       |                   | 2002 broiler line       |                   |
| Cumulative Mortality            | n <sup>1</sup> (N = 91) | %                 | n <sup>1</sup> (N = 42) | %                 | n <sup>1</sup> (N = 78) | %                 | n <sup>1</sup> (N = 97) | %                 |
| 28                              | 0                       | 0.0               | 1                       | 2.4               | 0                       | 0 <sup>a</sup>    | 2                       | 2.1 <sup>a</sup>  |
| 35                              | 5                       | 5.5               | 2                       | 4.8               | 3                       | 3.8 <sup>b</sup>  | 10                      | 10.3 <sup>a</sup> |
| 42                              | 10                      | 11.0 <sup>b</sup> | 9                       | 21.4 <sup>a</sup> | 12                      | 15.4 <sup>b</sup> | 26                      | 26.8 <sup>a</sup> |
| 54 <sup>2</sup>                 | 22                      | 24.2              | --                      | --                | 15                      | 19.2              | --                      | --                |
| Morbidity <sup>3</sup> 42 or 54 | 7                       | 7.6               | 4                       | 9.5               | 11                      | 14.1              | 20                      | 20.6              |
| Total AS incidence              | 29                      | 31.8              | 13                      | 31.0              | 26                      | 33.3              | 46                      | 47.4              |

<sup>a, b</sup> Mortality or morbidity percentages per line within rows (ages), within experimental year, without common superscript differ significantly ( $\chi^2$  test,  $P < 0.05$ )

<sup>1</sup> n = number of birds with AS; N = total number of birds in the line.

<sup>2</sup> The birds from the 1986 broiler line were kept under AIC through 54 d of age.

<sup>3</sup> Birds that survived to the end of trial (Day 54 for the 1986 broiler line; Day 42 for the 2002 and 2006 broiler lines) but were diagnosed with AS.

**Table 1.** Cumulative mortality and morbidity due to the ascites syndrome (AS) at various ages in broiler lines of the years 1986, 2002 and 2006, all reared together under high-challenge ascites-inducing conditions (AICs) from Day 19 to end of trial (According to [71]).

These results, supported by several previous studies [68,70-78], suggest that there is no "true" genetic correlation between the potential GR of broilers and their propensity to develop AS. It seems that AS is not caused by the increased O<sub>2</sub> requirement of a fast growth rate, but by an impairment of the O<sub>2</sub> supply needed to sustain the fast growth rate.

Thus, a better solution would be to select against AS susceptibility, because if all broilers were resistant to AS, management-induced reduction of growth rate would no longer be needed. Breeding against AS susceptibility should aim at identifying and eliminating all the AS-susceptible individuals in the selected population and selecting for high GR among the AS-resistant ones.

The questions raised by the last hypothesis concern what might cause broilers to be susceptible to ascites, and whether it is related to physiological disorders of the cardiovascular system.

This chapter will introduce readers to the physiological Ascites Syndrome and the complexity of the problems that highly productive broiler chickens face in coping with high-oxygen-demand conditions such as cold stress and high altitude. It will focus on: a. the ascites syndrome – its causes and etiology in broiler chickens; b. cardiovascular functioning and responsiveness in ascitic broilers; and c. genetic and physiological aspects of coping with the syndrome.

## 2. The Ascites syndrome: Its causes and etiology in broiler chickens

### *Ascites physiology and etiology:*

The AS involves accumulation of fluids in the abdominal cavity [79], which prompted the common name of “water belly” to describe the syndrome; it occurs when broilers fail to supply sufficient oxygen to support their metabolic demands [80]. In the late 1970s AS was observed only at high altitudes [81], but since then it has been found also at low altitudes [82], mainly in broilers reared at low ambient temperatures and/or fed pelleted feed with high energy content.

The general pathogenesis of AS has been well documented [52,54,83,84]. Rapid growth requires a high resting metabolic rate, which requires adequate O<sub>2</sub> supply and utilization. The broiler chicken probably has more genetic potential for growth than it has potential to provide O<sub>2</sub> to sustain that growth, and in some broilers the demand for O<sub>2</sub> might exceed the cardiopulmonary capacity to supply sufficient O<sub>2</sub>, ultimately leading to an O<sub>2</sub> deficit [85]. The heart responds by increasing its output of (deoxygenated) blood to the lungs for oxygenation. This increased blood flow causes an increase in the blood pressure required to push the blood through the capillaries in the lung which, in turn, causes pulmonary hypertension. This increase in work load results in an enhanced pressure load on the right ventricular muscle wall, to which the muscle cells respond by adding parallel sarcomeres, causing thickening (hypertrophy) of the right ventricular wall. The muscular right ventricular wall increases the pressure in the pulmonary arteries, arterioles and capillaries of the lung. This process continues, causing additional hypertrophy. Meanwhile, the right atrio-ventricular valve thickens and starts to leak, partly because the thicker valve is now less effective and partly because of the increasing back pressure from the pulmonary arteries and right ventricular chamber [86]. The leaking valve aggravates the excess pressure problem by admitting excess volume, the right ventricle dilates, and the wall-muscle cells lengthen by producing longitudinally arranged sarcomeres.

The increased blood volume raises the pressure overload until valve deficiency occurs, causing a drop in cardiac output and pulmonary hypertension, but marked pressure increases in the right atrium, sinus venosus, vena cava and portal vein. This increased pressure in the sinusoids of the liver causes leakage of plasma from the liver into the hepatoperitoneal spaces, i.e., ascites. The leaking valve and increased venous pressure result in hypoxemia and tissue hypoxia, and the kidney responds by producing erythropoietin in an attempt to increase the blood's O<sub>2</sub> carrying capacity by intensively producing more red blood cells.

Domestication had introduced several other insufficiencies into the cardiovascular system; among them is a thicker respiratory membrane than that in other birds, i.e., broilers have a thicker respiratory membrane than Leghorn-type laying fowl. This leads to: a. lower efficiency of O<sub>2</sub> transfer through the respiratory membrane; and b. lower hemoglobin oxygenation capability [62]. Research focusing on hemoglobin O<sub>2</sub> saturation in meat-type chickens indicated that fast-growing broilers have lower saturation than slow-

growing broilers [30,87]. These results suggested that some meat-type chickens were not fully oxygenating their hemoglobin, even at low altitude. This might have been the result of increased blood flow rate through the lung capillary bed, which would reduce the time available for hemoglobin to be oxygenated in the lung interface [32,88], or to presence of immature red blood cells in the system [89]. In order to overcome this situation an increase in erythropoiesis takes place. However, such an increase, if not coupled to plasma volume expansion would increase blood viscosity, followed by increased blood-flow resistance [90]. The back pressure in the veins causes venous congestion, dilation and prominent vessels [50]. The lack of O<sub>2</sub> in the heart muscle results in hypoxic damage and, finally, right-ventricular hypertrophy. As cardiac output is reduced and tissue hypoxia becomes worse, the left ventricle loses muscle mass, the wall thins (because of hypoxia and disuse atrophy), the valves thicken and the chamber enlarges. Heart muscle damage is caused by the excess workload and by the tissue hypoxia associated with circulatory failure, not by the tissue hypoxia that increases cardiac output and triggers pulmonary hypertension.

*Environmental causes of ascites syndrome:*

**Altitude:** The partial pressure of oxygen becomes lower with increasing altitude. The ability of chickens to oxygenate their hemoglobin fully as the erythrocytes pass through the lung depends on the transit time in the lung, hemoglobin- O<sub>2</sub> affinity, the thickness of the air-hemoglobin barrier and, especially, the partial pressure of O<sub>2</sub> in the air [62]. The effects of high altitude or hypoxia on ascites and heart disorders in broilers were reported as early as the 1950s and 1960s [91-97]. Those reports indicated that birds raised at high altitudes died because of right ventricular hypertrophy, congested and edematous lungs, and accumulation of fluid in the abdominal cavity. Significant microscopic damage to the heart, lungs and kidneys was also found in birds reared at high altitude [95,97], as well as in 1-week-old broilers raised at high altitude [98] and in birds exposed to simulated high altitude [99-101].

Because AS was first noticed in birds raised at high altitude, the use of natural or simulated high-altitude conditions was one of the first experimental protocols to be used [see, e.g., 47,97]. The hypobaric chamber has been shown to be an effective tool for simulating high altitude and consistently inducing AS [102-106]; it simulates high altitude conditions by generating a partial vacuum, thereby reducing the partial pressure of O<sub>2</sub>. Anthony and Balog [106], by simulating an altitude of 2,900 m above sea level, successfully induced 66% AS in a commercial sire line. In six lines of commercial broilers that were reared in the same hypobaric chamber, 47% of the birds developed AS [107].

When birds are exposed to low atmospheric O<sub>2</sub> levels pulmonary blood vessels constrict and pulmonary vascular resistance increases [108]. This immediate increase in pulmonary arterial pressure can, over time, cause right ventricular hypertrophy and eventually result in the ascites syndrome [81,89,109-111]. Additionally, hypoxemia leads to an increase in hematocrit, which, in turn, increases blood viscosity and results in increased resistance to blood flow through the pulmonary blood vessels [90,112-116].

**Low temperature:** Temperature is the most-studied environmental cause of ascites [see, e.g., 117-125]. In endothermic animals (mammals and birds) body temperature ( $T_b$ ) is the most physiologically protected parameter of the body; therefore, the thermoregulatory system in these animals operates at a very high gain, in order to hold  $T_b$  within a relatively narrow range, despite moderate to extreme changes in environmental conditions [126]. The ability to maintain a stable  $T_b$  springs from the mechanisms that control heat production and heat loss; mechanisms that changed in the course of evolution, to enable endothermia to replace ectothermia [127,128]. Birds mostly respond to acute or chronic cold exposure by increasing their metabolic rate and oxygen requirement [129,130]. It was reported that a drop in environmental temperature from 20 to 2°C almost doubled the oxygen requirement of White Leghorn hens [131], and in another study there was a 32.7% increase in oxygen requirement in response to low temperatures [132].

Low temperatures were found to increase ascites by increasing both metabolic  $O_2$  requirements and pulmonary hypertension [122,133]. This increase in pulmonary arterial pressure was attributed to a cold-induced increase in cardiac output, rather than to hypoxemic pulmonary vasoconstriction [134]. As a result, low ambient temperature has been widely used to induce AS in broilers [60,66,73,115,122,134-140]. Various protocols were developed, ranging from exposure to constant low temperatures [60,73,122,135,136,140], through gradual stepping down of ambient temperature [66,122,137,139], to episodic protocols under which the birds were exposed to natural fluctuations of winter temperatures [115,138]. The efficacy of a cold-exposure protocol depends upon its timing, duration and magnitude, as well as husbandry and the birds' genetic tendency to develop AS.

The effect of the timing of a cold-stress application on ascites development in broilers indicates that exposure to low temperatures during brooding has a long-lasting effect on ascites susceptibility [62,120,125,137,141,142]. The consensus appears to be that cold stress during the first two weeks of life affects the birds' metabolic rate for several weeks, and increases their susceptibility to ascites [62,120,125,137,141,142]. A novel AIC protocol for AS [72] involved rearing the tested birds in individual cages from 19 d of age, so that they could not escape the challenge of the environmental conditions, which comprised fan-induced air movement at about 2 m/s and moderately low ambient temperatures (18 to 20°C). The effects of the environmental conditions were augmented by early use of high-energy pelleted feed to enhance rapid growth and by lighting for 23 h/d. Under this combination of conditions, %AS among the broilers was 44% – much higher than those reported for cold-stressed broilers on litter, and similar to or slightly lower than that among broilers challenged by hypobaric chamber.

The birds that developed ascites as a result of exposure to low temperatures exhibited the same pathological symptoms as those that developed it under low  $O_2$  partial pressure – symptoms including increased hematocrit, hemoglobin, heart weight, and right-ventricle:total-ventricle ratios [70-72,122,124,143-147].

### 3. Cardiovascular functioning and responsiveness in ascitic broilers

#### *Blood O<sub>2</sub> transport, erythropoiesis and ascites*

The blood system provides the main systemic response to environmental changes and metabolic demands, either through the cardiovascular system or through alteration in O<sub>2</sub>-carrying capacity.

Reduced O<sub>2</sub> availability in the blood (hypoxemia), reduces the O<sub>2</sub> partial pressure (PO<sub>2</sub>) of the arterial blood (PaO<sub>2</sub>). In such a situation the blood system must maintain an adequate delivery of O<sub>2</sub> to the peripheral tissues, while maintaining an adequate PO<sub>2</sub> at the vascular supply source,, in order to permit O<sub>2</sub> diffusion to the tissue mitochondria.

Oxygen delivery can be enhanced by increasing the total cardiac output (Q) and by increasing the blood O<sub>2</sub> capacitance coefficient ( $\beta_{bO_2}$ ). The latter parameter is defined as the ratio  $(CaO_2 - CvO_2)/(PaO_2 - PvO_2)$ , where  $CaO_2 - CvO_2$  is the arterial-venous difference in O<sub>2</sub> concentration and  $PaO_2 - PvO_2$  is the arterial-venous difference in PO<sub>2</sub>.

With regard to maintaining an adequate PO<sub>2</sub> at the vascular supply source, the lower critical PO<sub>2</sub> can be expressed as  $PvO_2 = PaO_2 - [\beta_{bO_2} \times (Q/VO_2)] - 1$ , in which VO<sub>2</sub> is the rate of O<sub>2</sub> consumption by the tissues and the product  $\beta_{bO_2} \times (Q/VO_2)$  is the specific blood O<sub>2</sub> conductance [148,149]. Because PaO<sub>2</sub> is determined by ventilation and O<sub>2</sub> equilibration at the blood-gas interface, this equation shows that an increase in specific blood-O<sub>2</sub> conductance minimizes the decline in PvO<sub>2</sub> under hypoxia, thereby maintaining an adequate pressure head for O<sub>2</sub> diffusion to the tissue mitochondria [2].

Under severe hypoxia, an increased blood-O<sub>2</sub> affinity will tend to maximize  $\beta_{bO_2}$ . The resultant increase in the specific blood O<sub>2</sub> conductance helps meet challenges of both delivery and supply: it minimizes the expected PO<sub>2</sub> decrement in the tissue capillaries while preserving a constant  $CaO_2 - CvO_2$  difference. Likewise, an increased hemoglobin concentration increases  $CaO_2$ , thereby increasing blood O<sub>2</sub> conductance if PaO<sub>2</sub>, Q and VO<sub>2</sub> all remain constant. With excessive polycythemia, however, potential advantages of an increased Hb concentration for O<sub>2</sub>-carrying capacity might be more than offset by a corresponding reduction in Q.

Several significant alterations to the blood system in AS broilers were well documented: increased red blood cell numbers, through increased erythropoietin production [96,100,150-153]; elevation of hematocrit values and blood viscosity [54,72,154], and central venous blood congestion [50,155]. These findings raised the question of the association between the plasma and the fluid that accumulated in the abdominal cavity, and whether the increase in hematocrit resulted from a decline in plasma volume caused by plasma leakage out of the blood vessels, or from increased erythropoiesis that occurred as a compensatory reaction to the lack of oxygen in the tissue. In ascitic broilers the composition of the abdominal cavity fluid was fairly similar to that of the plasma, with regard to osmolality, and total protein and albumin concentrations, which suggests a deficiency in the selective permeability of the blood vessels [89]. These findings resemble those in cirrhotic human patients with ascites

[156-158]. The escape of plasma fluid out of the blood vessels was probably due to increased pulmonary hypertension and central venous congestion – symptoms found both in humans [158] and in broilers [56]. As in the case of human ascitic patients [159], AS broilers exhibited conservation of plasma volume similar to that of the healthy ones. However, the PCV in the AS broilers increased significantly, by up to 80%, as a result of a significant increase in the number of erythrocytes, which also contributed to a significant elevation in blood volume. Thus, enhanced erythropoiesis, and not plasma volume reduction, was found to be involved in the hemodynamics of the ascitic broilers [89]. This finding could also account for the blood congestion and the increased blood viscosity [90] that contribute to the enhanced cardiac workload [103,134], blood pressure [103], and blood-flow resistance [111] in AS chickens.

In AS birds, the high PCV, on the one hand, and the significant decline in blood oxygen saturation, on the other hand [30,57,66] raised the possibility of an impairment of blood O<sub>2</sub>-carrying capacity. Increased erythrocyte rigidity appears to be another important factor in AS [54,62,113]: the nucleated erythrocytes will normally curl or fold to pass through lung capillaries [160], but hypoxemia and high hemoglobin concentrations decrease the deformability of erythrocytes [62]. Further calculations of hemoglobin content per 1,000 red blood cells revealed a significant reduction in the AS broilers compared with that in the healthy and control broilers [57,89]. These results suggest the possibility of inefficient enhancement of the erythropoiesis process.

Ascites-induction conditions elicited enhanced erythropoiesis, which resulted in an increased proportion of immature erythrocytes in the bloodstream. However, whereas in the healthy broilers only a moderate proportion (7.2%) of immature erythrocytes was observed, in the AS ones, immature erythrocytes contributed up to 23.5% to the total erythrocyte count [89]. The significant increase in immature erythrocytes, coupled with the significant decline in hemoglobin content, might provide the explanation for the decline of O<sub>2</sub> saturation in the blood of AS broilers [30,57,72,134].

The differences between healthy and AS chickens in their production of erythrocytes in general, and of immature erythrocytes in particular, suggest that erythropoiesis regulation in the ascitic birds is defective.

#### *The heart*

The avian heart is different from that of mammals in that the right atrio-ventricular valve is composed of a muscle loop made up mainly of muscle fibers from the right ventricle wall. The anatomy of this valve makes birds very susceptible to valve insufficiency [52,161,162]: when the right ventricle responds to an increased workload it becomes hypertrophic and the valve hypertrophies along with the ventricle [161]. This thickening of the valve interferes with its effectiveness and may lead to rapidly developing valve failure and ascites [161]. Although litter oiling did not reduce the average ascites score, litter oiling improved air quality significantly in the pens and also improved heart morphology by reducing the right ventricle area from 0.44 to 0.36 cm<sup>2</sup> in ad libitum birds [163, 164].

Alterations in the electrocardiogram (ECG) are seen in conjunction with AS. Of most importance has been the finding that increased S-wave amplitude in standard limb lead II indicates increased susceptibility to AS [111]. However, there were no ECG readings indicative of primary pulmonary hypertension in most birds that developed ascites [165]. A slower heart rate (bradycardia) [55,116], as well as reduction in the pulse rate had been found in birds developing AS [55] and in acutely cold-exposed birds [116].

Heart rate on days 1 and 7 was found to be significantly higher in the AS-susceptible (AS-S) genetic broiler line than in the AS-resistant (AS-R) broiler line, with only the lowest quartile of individual heart rates in the AS-S line overlapping the highest quartile in the AS-R line [57]. These results were in agreement with those of Druyan et al. [166], who found that generation S3 chicks from their AS-S line had a significantly higher heart rate on day of hatch than that of generation S3 chicks from the AS-R line. It was reported [167] that heart rate began to increase shortly after hatch, and reached a peak close to 4 wk of age; thereafter, it declined slowly [168]. The AS-S selected line exhibited increased heart rate only between d 1 and d 7, with a decline thereafter toward d 17, while the birds were kept under standard brooding condition [57]. Mild hypoxia was found to elicit an increase in heart rate [169,170], which suggests that the AS-S birds in that study experienced O<sub>2</sub> shortage already at the time of hatch, even when kept under optimal conditions. A higher mean partial pressure of CO<sub>2</sub> in broilers' venous blood (a marker for lung ventilation rate) on d 11 was found to be associated with increased ascites susceptibility [171,172]. Those results indicate that AS-susceptible birds suffer O<sub>2</sub> shortage at an early age. However, it also suggests that as long as the susceptible birds are under SBC, higher heart rate can compensate for a mild hypoxemia, and no other physiological parameter would be affected.

#### *Effect on heart and blood vessels*

Birds with ascites induced by either low ventilation or cold temperatures exhibited hypertrophy of the medial layer of arteriols, which was probably a response to primary pulmonary hypertension [173]. In low, ventilation-induced ascites, the broilers had significant inflammation or osseous-nodule formation in the lungs [174,175], whereas in cold-stress-induced ascites, birds showed no inflammation [173]. Wideman et al. [50] suggested that increases in pulmonary vascular resistance initiate increases in venous pressure by challenging the capacity of the right ventricle to thrust all the returning venous blood through the lungs. An acute reversal of systemic hypoxemia was reported to have no effect on pulmonary hypertension – a finding that discounted the influence of hypoxic pulmonary vasoconstriction [176]. It was hypothesized that this reversal of systemic hypoxemia increased total peripheral resistance and normalized arterial pressure and cardiac output, but could not decrease pulmonary hypertension because of the overwhelming influence of sustained pulmonary vascular resistance [176]. Development of techniques to measure changes in pulmonary arterial pressure and changes in wedge pressure helped to clarify that changes in pulmonary arterial pressure contribute to the mismatch between pulmonary vascular capacity and cardiac output, and that pulmonary hypertension is initiated as a consequence of excessive pulmonary arterial or arteriolar resistance [177,178]. The difference between individual broilers' susceptibility to ascites may

be related to an innate or acquired variability in their pulmonary vascular responsiveness to vasoactive mediators [179].

#### 4. Genetic and physiological aspects of coping with the syndrome

##### *The genetic control of susceptibility to AS*

Recent reports [71,72,107] indicate that about 50% of the broilers in commercial stocks develop AS under experimental protocols of high-challenge AIC. The term “high challenge” is used for AICs that apparently induce AS in all AS-susceptible individuals, whereas “low-challenge” AICs induce lower rates of AS, probably only in the AS-S individuals whose higher growth rates necessitate higher O<sub>2</sub> demands. The rates of AS reported in recent years are similar to those found under high-challenge AIC in the 1990s [68,73]. In recent years, however, actual AS mortality in commercial flocks has been significantly reduced or even completely eliminated by management practices that reduce feed intake and growth rate and, consequently, reduce the physiological O<sub>2</sub> demand [47,62]. The problem with this approach is that it compromises the efficiency of broiler production.

A better solution would be to select against AS susceptibility: once all the broilers were resistant to AS, a managed reduction in growth rate would no longer be needed. However, breeding is feasible only if there is an inherent susceptibility to AS and if effective selection against it can be applied.

Several studies have found the tendency of broilers to develop AS to be under genetic control, with estimates of heritability ranging from 0.1 to 0.7 [72-74,180,181]. Significant heritability of 0.5 to 0.6 has also been found for the ratio of right ventricle weight to total ventricle weight (RV:TV) – a postmortem indicator for AS development and severity [72-74,182]. These data indicate the feasibility of selecting against susceptibility to AS, but only if all the genetically susceptible birds are identified at the phenotypic level. Mortality or morbidity caused by AS provides the ultimate identification of AS-S individuals.

However, actual development of AS in susceptible birds depends on environmental conditions that lead to hypoxemia, either by reducing O<sub>2</sub> supply or increasing the O<sub>2</sub> demand [62]. It was found that a hypobaric chamber with a reduced O<sub>2</sub> partial pressure, equivalent to that at 2,900 m above sea level, successfully induced 66% AS in a commercial sire line, suggesting full exposure of genetic variation in AS susceptibility [103]. Surgical inactivation of one lung induced AS in all or most of the susceptible individuals [32,68,183,184]. The AIC protocol for broilers housed in individual cages, where the tested broilers could not avoid the environmental conditions that were based on movement of cool air driven by a fan, combined with high-energy pelleted feed and 23 h of light per day, resulted in about 50% AS among commercial broilers [70-72], suggesting that all or, at least, most of the susceptible broilers developed AS.

The successful induction of AS by means of any of these approaches suggests that breeding for AS resistance can be achieved by keeping all selection candidates under high-challenge AIC and awaiting mortality of all susceptible individuals. However, this direct-selection

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 than 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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 SaO<sub>2</sub>, as measured in selection candidates at 5 wk of age [187]. However, because of the low %AS in these unstressed flocks, high SaO<sub>2</sub> levels are expected in susceptible individuals that do not develop AS; also, low heritability (0.15) was reported for SaO<sub>2</sub> 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<sub>2</sub> 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 (14°C) 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<sub>2</sub>) [188], a trait known to be closely related to the AS [30,72]. Data on SaO<sub>2</sub> 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<sub>2</sub>, with high levels of SaO<sub>2</sub> 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<sub>2</sub> – a demand that might exceed the cardiovascular

system's capacity to satisfy the O<sub>2</sub> 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<sub>2</sub>, 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.

## Author details

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