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Cardiovascular biomarkers of high altitude adaptation: Selection aid for livestock breeding

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Abstract: The efficiency of oxygen usage and energy metabolism is important for high altitude adaptation and optimum performance of animals. With regards to adaptation and productivity of high yielder animals, high-altitude stress (hypobaric-hypoxia, cold stress) is a primary concern at high altitude. Cardiovascular system is an essential link in the transport of oxygen from the air to the mitochondria, and it therefore has an important role in acclimatization and adaptation to the oxygen depleted environment of high altitude. These pathophysiological changes belong to the morphological, functional, and component of cardiovascular system which can be detected as the biomarker whenever changes are found in this system. These cardiovascular biomarkers are structural, hematological, biochemical, molecular, and genetic. This lecture has reviewed the different types of cardiovascular biomarkers which are important in high altitude adaptation and therefore may be helpful in selection of adapted animals for future breeding and rearing at high altitude. Some structural biomarkers are hypertrophy of auricle and ventricle, pulmonary arterial pressure, hypertension, myocardial contractibility, hydrothorax, ascites, etc., whereas hematocrit levels, blood viscosity, plateletatic, are hematological biomarkers. Cardiac troponin-I and troponin-T, brain natriuretic peptide (BNP), inflammatory markers, rennin, etc. are biochemical biomarkers. Details of these biomarkers and other related markers will be discussed in present lecture. These biomarkers concentration or levels are indicator of physiological state genetic make-up of animals of respective environmental condition. Hence, these biomarkers along with performance and physical traits may be considered for selection high altitude adapted animals for breeding and rearing.

Key words: Animal adaptation; Cardiovascular system; Biomarkers; High altitude; Hypobaric hypoxia

Introduction

High Altitude (HA) environment is characterized by hypobaric hypoxia, extreme temperature variation, low humidity, intense ultra-violet radiation, low rain fall, and high wind velocity. Physiologically this environment is not suitable for better health and performance of animals and human beings. Native animals are more adapted to this environment as compared to non-native, but have low productivity. Since, maximum portion of basal energy is converted towards catabolism and maintenance of basal metabolic rate to cope this extreme clime, and so minimal energy is left for anabolic reaction and cellular metabolism. Hence, native animals are low productive and are in poor health condition. Therefore, there is need of selection and breeding of elite animals having more adaptability and productivity for this region.

Recent investigations are focused on identification of biomarkers of high altitude stress, productivity, and different metabolic diseases. Biomarkers are defined as a distinctive biological indicator of physiological processes or pathophysiological processes that occur with disease. In veterinary medicine and physiology, there has been a need to discover novel cardiovascular biomarkers to aid in the early detection, diagnosis, and prognosis of high altitude diseases in animals. Earlier several researchers indicated studies of cardiovascular biomarkers are important for selection of animals for high altitude areas. Our group, at Defence Institute of High Altitude Research (DIHAR), a high-altitude research station and at Defence Institute of Physiology and Allied Sciences (DIPAS), Delhi are the pioneer group in India working on high altitude adaptation and different physiological biomarkers of adaptation in domestic animals, laboratory animals in rodent species, and human. In this lecture, we reviewed our studies and other findings on cardiovascular biomarkers and how it could be useful in selection of elite animals. Among these biomarkers, hematocrit, platelets count, hypertension, blood viscosity, hydrothorax, ascites, pulmonary arterial pressure (PAP), cardiac troponin I (cTnI), creatine kinase myocardial b-fraction (CK-MB), rennin, IL-6, etc. are some of the sensitive and specific indicators for cardiovascular pathophysiology (1-7). Therefore, there are need to identify the suitable biomarkers

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so that it can be included in selection aids for selection of adapted and high producing animals for high altitude.

Cardiovascular physiology at high altitude environment

Due to hypobaric-hypoxia at HA, pulmonary blood flow is greatly affected. The lower air pressure makes it more difficult for oxygen to enter our vascular systems (Fig. 1). The result is hypoxia, or oxygen deprivation. Animal body has a series of physiological adjustments to compensate this hypoxia including increase in ventilation, hemodynamic and hematologic changes, metabolic changes, cardiovascular morphological and functional changes which are usually termed as acclimatization (8, 9). However, in susceptible animals this causes an increase in pulmonary arterial pressure, stress on the right ventricle, congestive right heart failure, and hydrothorax in the chest cavity and brisket disease. Upon initial exposure to HA, initial transient increase in erythrocyte concentration can be seen which is caused by a reduced plasma volume, not by an increased rate of erythrocyte production (9). In a sequel, this caused in increasing the blood viscosity. Elevated blood viscosity as a result of polycythemia is an additional determinant of pulmonary artery hypertrophy (10). At this time, there are several hematological, immunological, molecular, and genetic biomarkers levels are changed.

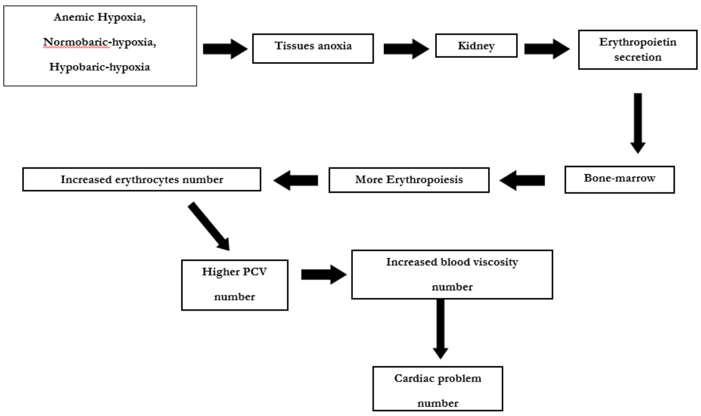

Figure 1: Diagrammatic representation of different hematological parameters involved in pathophysiology of cardiac problem

We frequently observe ascites, congestive heart failure (CHF), urinary retention, pulmonary edema, hydropericardium, hydrothorax, etc. during postmortem of exotic poultry, sheep, cattle, and goat breeds but not in Yak and local breed of animals (11, 12). Therefore, when we bring lowlanders/exotic animals for breeding purpose to produce more from local through up-gradation of local breed of animals, their bodies initially develop inefficient physiological responses and if persist they develop high altitude maladies in high altitude susceptible animals. Hematological, physiological response, and biochemical biomarkers studied are significant indicative of pathophysiological change (11, 12).

Hematological marker of cardiovascular physiology at high altitude

Transport of O_2 in the blood is mainly carried out by hemoglobin (Hb) which is present in RBCs. Upon initial exposure to high altitude, initial transient increase in hematocrit and erythrocyte concentration can be seen which is caused by a reduced plasma volume, not by an increased rate of erythrocyte production (9, 12). Body water distribution has influence on Hb and hematocrit values during a long-term exposure at high altitude. Tannheimer *et al.,* (13) study findings indicated rapid massive increase of Hb and hematocrit at altitude due intravascular hemo-concentration effect provoked by a shift of fluid to the interstitium.

O_2 concentration in the blood is also maintained with the changes in the affinity for O_2. The affinity for O_2 depends mainly on the acid-base status and the total concentration of organic phosphates in the erythrocyte, mainly 2, 3-diphosphoglycerate (DPG) and ATP (14). DPG binds to Hb and decreases its affinity for O_2 on exposure to high altitude. It was found that RBC-DPG increased, but the predicted rightward shift was counterbalanced by an increasing blood pH with increasing altitude. Relative increasing in capillary bed may lead to better blood perfusion and, thus, O_2 could more readily diffuse despite the relatively low O_2 concentration (9, 15).

Biochemical and molecular biomarkers of cardiovascular patho-physiology

Different biochemical molecular biomarkers are presented in Table 1, viz. cardiac natriuretic peptides (NPs), soluble CD40 ligand, NT-proBNP and BNP (brain natriuretic peptide), troponin-I, troponin-T, plasminogen activator inhibitor-1, etc. which are indicator of congestive cardiac failure which are prevalent in high altitude region (Table 1) (10, 16, 17). Measurement of C-reactive protein using highly sensitive assays (hsCRP) has revealed the association between hsCRP and future vascular events such as myocardial infarction in healthy populations, as well as adding to the risk stratification of those suffering acute coronary syndromes (18). Natriuretic peptides (NP) release may also be stimulated by hypoxia (19) and they have been found to be elevated in association with pulmonary artery hypertension (20, 21) at sea-level (SL). High altitude pulmonary edema (HAPE) is a noncardiogenic form of pulmonary edema, a central feature of which is an exaggerated pulmonary vascular response with a marked rise in pulmonary artery systolic pressure (PASP) (22). Therefore, measurement of these biomarkers may give insight of animal adaptation to high altitude. However, their levels are to normalize in different species and pathological conditions before associating with markers of high altitude related disease in animals.

Table 1: Different biomarkers associated with pathophysiology of cardiovascular system.

Arterial vulnerability				
Serological biomarkers of arterial vulnerability	**Cardiac muscle inflammation**	**Structural and functional markers of arterial vulnerability**	**Blood vulnerability**	**Myocardial vulnerability**
Lipid profile, Apo B, Lp(a), LDL, CETP, Lp-PLA2.	C-reactive protein, Lipoprotein-associated phospholipase A2, HsCRP, sICAM-1, IL-6, IL-18, SAA, MPO, sCD40, Oxidized LDL, GPX1 activity, Nitrotyrosine, Cystatin-C, ADMA, MMP-9, IMP-1.	Blood pressure, Hydrothorax, Carotid IMT, Coronary artery calcium, Arterial stiffness, Homocysteine, Urine albumin, Renin.	Fibrinogen, Coagulation factors, Platelets no., Heamatocrit, Plasminogen-activator inhibitor 1.	LVH, LV dysfunction, Cardiac troponin-I and troponin-T for myocardial infarction, Myocardial contractibility, Brain natriuretic peptide (BNP) for heart failure.

Abbreviations: ADMA: asymmetrical dimethyl arginine; Apo B: apolipoprotein B; CETP: cholesterol ester transfer protein; GPX1: glutathione peroxidase; IL: interleukin; IMT: intimal-medial thickness; Lp(a): lipoprotein a; LpPLA2: lipoprotein-associated phospholipase A2; LV: left ventricle; LVH: LV hypertrophy; MMP: matrix metalloproteinase; MPO: myeloperoxidase; SAA: serum amyloid A; sCD40L: soluble CD40 ligand; sICAM: soluble intercellular adhesion molecule; PAI-1, plasminogen activator inhibitor 1; TIMP, tissue inhibitor of matrix metalloproteinases; and TPA, tissue plasminogen activator (1-4, 6).

Associated genetic markers of cardiovascular physiology of high altitude adaptation

Animals like snow leopards, yaks, tibetan wild bores, native livestock species, and as well as human beings have adapted to the chronic hypoxia of high altitude in several locations. High-altitude adaptation may be due to multiple genes that act in concert with one another. The recent genomic studies have indicated a genetic basis for the alteration in expression of some cardiovascular system related biomarkers. Among them, hypoxia inducible factor (HIF) is most important which control transcriptional response to hypoxia (23, 24).

Cardiovascular biomarkers as selection aid for livestock

Physio-biochemical and molecular biomarkers also provide an opportunity to assess the causality of biomarkers for disease and adaptation to specific environment. Therefore, these biomarkers can be included while selection of animals along with other phenotypic traits. However, this has not been practiced for animal selection in large due to unavailability of universal markers and their level of different animal species. Therefore, many studies have been started on association studies among genetic polymorphism, genetic markers, phenotypic traits, and these physio-biochemical biomarkers. One of our studies on relationship among some biochemical and antioxidant indices, and phenotypic traits indicated significant relationship among these parameters in different breeds of goats at high altitude (Unpublished data). Hence, it is concluded that these biomarkers may be helpful in selection of elite animals.

Conclusions

In summary, changes in the cardiovascular system during hypobaric hypoxia have been observed not only in the functional state of the heart and vascular system but also in the cellular and sub-cellular structures, leading to long term adaptation. These pathophysiological changes are characterized by cardiac function indices and presence of biomarkers in blood vascular system, and structural changes in related organs. Present lecture highlighted the important cardiovascular biomarkers of high altitude adaptation and how they will be useful in selection and breeding for production of elite germplasm for high altitude areas. However, these biomarkers may not be useful in selection, as some biomarkers can underscore the importance of a biological pathway and might not provide a substantial increase in predictive value. Therefore, prerequisite for the practical and clinical use of biomarkers in selection and prediction of disease is elucidation of the specific indications, standardization of analytical methods, characterization of analytical features, assessment of performance parameters for the given species, physiological state, and demonstration of cost-effectiveness. However, technological advances will likely facilitate the use of multi-biomarker profiling along with physical traits in selection of animals and identification of more adapted animals to high altitude.

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