Cardiac involvement in canine babesiosis

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ABSTRACT

Cardiac dysfunction in canine babesiosis has traditionally been regarded as a rare complication, with the majority of lesions reported as incidental findings at *post-mortem* examination. Recent studies have, however, demonstrated cardiac lesions in canine babesiosis. Cardiac troponins, especially troponin I, are sensitive markers of myocardial injury in canine babesiosis, and the magnitude of elevation of plasma troponin I concentrations appears to be proportional to the severity of the disease. ECG changes in babesiosis are similar to the pattern described for myocarditis and myocardial ischaemia and together with histopathological findings indicate that the heart suffers from the same pathological processes described in other organs in canine babesiosis, namely inflammation and hypoxia. The clinical application of the ECG appears to be limited and thus cardiovascular assessment should be based on functional monitoring rather than an ECG tracing. On cardiac histopathology from dogs that succumbed to babesiosis, haemorrhage, necrosis, inflammation and fibrin microthrombi in the myocardium were documented, all of which would have resulted in ECG changes and elevations in cardiac troponin. Myocardial damage causes left ventricular failure, which will result in hypotension and an expansion of the plasma volume due to homeostatic mechanisms.

Key words: *Babesia canis,* complication, dog, heart, therapy, troponin.

Lobetti R G **Cardiac dysfunction in canine babesiosis**. *Journal of the South African Veterinary Association* (2005) 76(1): 4–8 (En.). Bryanston Veterinary Hospital, PO Box 67092, Bryanston, 2021 South Africa.

INTRODUCTION

Canine babesiosis is an extremely common tick-borne disease throughout South Africa. In a survey done approximately 10 years ago, the results showed that on average, a veterinary practice treats between 100 and 500 babesiosis cases each year[8]. The average number of canine babesiosis cases at the Onderstepoort Veterinary Academic Hospital (OVAH) from 1988 to 1993 was 1253 per year, which represented 11.69 % of all dogs presented to the OVAH[38].

The parasites *Babesia canis* and *B. gibsoni* are responsible for canine babesiosis throughout the world. There are 3 subspecies of *B. canis,* namely *B. c. canis, B. c. vogeli,* and *B. c. rossi*[46]. *Babesia c. canis* is found in Europe, *B. c. vogeli* in northern Africa, North America and South Africa[27] and *B. c. rossi* in southern Africa[41,46]. *Babesia gibsoni* is subdivided into 2 subspecies: the North American and Asian subspecies[48].

Canine babesiosis can be clinically classified as uncomplicated or complicated[16]. Uncomplicated babesiosis is further divided into mild, moderate, or severe disease, depending on the severity of anaemia[16]. Mild uncomplicated babesiosis can progress to severe uncomplicated disease, in which anaemia can become life-threatening. Complicated babesiosis involves clinical manifestations that are unrelated to haemolytic disease. Common complications are acute renal failure, cerebral babesiosis, coagulopathy, icterus and hepatopathy, immune-mediated haemolytic anaemia (IMHA), peracute babesiosis, acute respiratory distress syndrome (ARDS), haemoconcentration, hypotension, pancreatitis and shock[16,21]. Different complications can overlap.

Heart lesions have been reported as incidental findings at *post-mortem* examination of complicated babesiosis cases[29] and thus considered a rare complication of babesiosis[16,21]. To date, however, the prevalence has been poorly described. Lesions that have been observed are foci of myocardial necrosis with macrophage and neutrophil infiltration (unpubl. data, Pathology Section, Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria), and subepicardial and subendocardial haemorrhages, micro-thrombi of the myocardium[29,42], hydropericardium and haemopericardium[29,33,42]. Dilated cardiac blood vessels containing considerable numbers of parasitised erythrocytes and free parasites have been reported[26]. In bovine and equine babesiosis, ecchymotic haemorrhages in the epicardium, endocardium and myocardium have been described[15]. These cardiac lesions probably develop due to one or both of the mechanisms postulated for tissue damage in babesiosis, namely an overwhelming inflammatory response and anaemic hypoxia[32].

This paper reviews the cardiac dysfunction and pathology that can occur with canine babesiosis, classifies it as an important complication of babesiosis, and briefly outlines the supportive therapy.

CARDIAC ASSESSMENT

Myocardial cell injury has recently been documented in canine babesiosis, as dogs that died naturally of disease had myocardial lesions as well as higher concentrations of cardiac troponins in plasma than did those that survived[24]. Cardiac troponins I (cTnI) and T (cTnT)) are important cardiac biomarkers in humans as they represent a highly sensitive marker for myocardial cell death[19]. In human cardiology, they are the test of choice for the diagnosis of myocardial infarction[9,44]. The amino acid sequence of cardiac troponins in humans and dogs is nearly identical because troponins are phylogenetically highly conserved proteins in mammals and myocardial concentrations of cardiac troponins in man and dogs are similar[30]. The cardiac troponin immunoassay developed for diagnosis of cardiac injury in humans is useful across a wide range of species. Cardiac troponins are thin, filament-associated proteins of cardiac muscle that act as the regulatory subunit of the troponin complex associated with the actin thin filament within muscle cells. Troponins are integral in the regulation of muscle contraction[31]. The diagnostic time window of these markers in humans is wide, being up to 72 hours[9]. The markers have 100 % sensitivity and 97 % specificity for diagnosing acute myocardial infarction 12 hours after presentation to hospital, and concentrations remain raised for as long as 10 days[9]. In babesiosis, the dog will have been ill for more than 8 hours but usually not for longer than 10 days before presentation[21], which makes the determination of

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Received: September 2004. Accepted: February 2005.

cardiac troponin concentrations ideal for establishing the presence or absence of myocardial injury.

Cardiac troponins are a more sensitive and persistent indicator of cardiac injury, with high tissue specificity, than other markers in the presence of marked skeletal muscle injury, liver disease, and chronic renal failure[28,30,35] This is an important consideration in babesiosis, especially the complicated forms, in which renal failure, liver impairment, and rhabdomyolysis can occur[16,21]. In babesiosis, the diagnostic sensitivity of cTnT to detect myocardial damage is less than that of cTnI, which is in agreement with a previous study in dogs[37]. Following myocardial contusion in the dog, it has been shown that the analysis of serum cTnI is more sensitive in detecting myocardial abnormalities than determination of lactate dehydrogenase (LD), creatine kinase (CK), α-hydroxybutyrate dehydrogenase (α-HBDH), MB isoenzyme of CK (CK-MB) or ECG[37]. Aspartate aminotransferase, myoglobin, LD, CK, or α-HBDH are very sensitive markers of myocardial cell damage, but lack cardiac specificity[37]. In babesiosis these variables could also be falsely elevated due to both muscle and liver pathology. A variable of higher specificity for myocardial cell injury in man is the CK-MB. However, the CK-MB isoform in the canine myocardium represents only 4–13 % of the total cardiac CK activity, compared with an average of 40% in man[4]. Other sources of CK-MB in dogs are the spleen, muscle, lungs, and intestinal tissue[4], all of which can be affected in canine babesiosis.

In humans, cardiac troponin I has been shown to accurately detect cardiac contusions, with a greater sensitivity than transthoracic echocardiography, and it can detect myocardial injury in the absence of diagnostic ECG abnormalities[3]. A similar finding has been reported in dogs with blunt thoracic trauma[37]. Following cardiac contusions the resultant ischaemia, cytokine release, autonomic dysbalance, reperfusion injury, and/or acid-base and electrolyte derangements may all result in diminished myocardial performance or cardiac arrhythmias. As anaemic hypoxia, and acid-base and electrolyte derangements occur in babesiosis[16,21], it is likely that myocardial integrity is also compromised in this disease.

Myocardial cell damage may be present even in the absence of histological signs of myocarditis with additional immunohistologic analysis often showing lymphocytic infiltrates and elevated concentrations of cTnT being highly predictive for myocarditis in these patients[20]. In dogs with babesiosis[11], multifocal myocardial necrosis and secondary inflammation has been reported. In man, cardiac troponins are the preferred biomarker to detect microscopic zones of myocardial necrosis with almost absolute specificity and sensitivity[44]. Endocardial biopsy is the antemortem gold standard method to diagnose myocarditis[39]. However, this is a very invasive method, and it is not practical in critically ill babesiosis cases. As cTnI has been shown to be elevated in myocarditis[40], it can assist in making this diagnosis in canine babesiosis.

Dogs with babesiosis that showed histological myocardial lesions in 1 study[11] had elevated cardiac troponin concentrations[24]. Although the numbers were small, the results of that study suggested the possibility that an increase in cTnI concentration may be associated with a poor outcome, with all non-survivors having elevated cTnI concentration. It has been shown that high and persistently elevated concentrations of cTnI reflect ongoing cardiac damage[19,44]. Thus, cardiac troponins appear to be sensitive markers of myocardial injury in this disease and the magnitude of elevation of plasma troponins concentrations appears to be proportional to the severity of the disease.

One study showed that dogs with babesiosis can develop a variety of ECG changes, namely prolonged QRS duration, ST deviation, coving, and prolongation, notching of the R-wave, first degree atrio-ventricular (AV) block, sinoatrial (SA) block, escape rhythms, VPCs, and ventricular tachycardia[11]. In the latter study, with the exception of VPCs, the incidence of the ECG changes was not higher in dogs with complicated babesiosis or those succumbing to the disease. In addition there was not a clear-cut relationship between ECG changes and myocardial injury. The presence of VPCs was associated with elevated cTnI concentrations[24]. The presence of VPCs as an indicator of myocardial damage on an ECG appeared to have high specificity but low sensitivity. The sensitivity and specificity of the ECG to diagnose myocardial damage may be improved by longer and more frequent ECG recordings and/or by the use of 24-hour Holter recordings. Notching of the R wave can be indicative of myocardial infarction[45]. In babesiosis notching of the R wave appears to be an inconsistent finding; however, it was more commonly seen in dogs with secondary IMHA[11]. Primary IMHA has been shown to predispose dogs to thrombo-embolic disease and myocardial infarction[12].

In babesiosis there is no apparent correlation between ECG changes and histopathological changes[11]. This reflects the non-specific properties of the ECG, which cannot differentiate cardiac and extracardiac causes of altered heart conduction, as well as the fact that the numbers of necropsies in clinical studies is always limited. Heart pathology is also often non-specific, since there are similar changes involved in many disease and agonal processes[34,47]. The changes seen in these studies are multifactorial and canine babesiosis has a variety of metabolic and pathologic abnormalities that can contribute to both ECG and pathological changes[16,47].

In a recent study[17], it was shown that hypotension occurs frequently in babesiosis and that the presence and severity of hypotension increases with increased disease severity. The possible causes for the hypotension have been speculated to be increased capillary permeability with movement of fluid to the interstitium, reduced vascular tone with venous pooling, and myocardial depression. Myocardial infarction will result in both vascular pooling and myocardial depression. Thus, a feasible explanation for the hypotension in canine babesiosis would be myocardial pathology.

Increased plasma volume has been speculated in canine babesiosis[36] and reported in malaria[1], possibly due to movement of interstitial fluid into the vasculature secondary to hypotension[36] and with evidence of increased blood volume in the presence of hypotension in some patients with malaria[39]. The pathogenesis of this phenomenon is thought to be reduction of effective blood volume – through peripheral vasodilation, (mediated by nitric oxide), followed by the release of vasopressors, noradrenalin, renin activation, and reduced renal haemodynamics[39].

Hypoalbuminaemia has been reported in canine babesiosis[22], which may either be because of intravascular volume dilution due to fluid retention or being a negative acute phase protein. As babesiosis is an acute disease, decreased albumin production from the liver would be a very unlikely cause for the hypoalbuminaemia. In the light of the cardiac changes and hypotension, a probable cause would be fluid retention due to myocardial disease. In humans it has been shown that hypoalbuminaemia can cause interstitial oedema[10]. Patients with malaria, where the pulmonary capillary wedge pressure has been assessed using a Swan-Ganz catheter, have an increased pressure that would be suggestive of either a cardiogenic or hypervolaemic mechanism[5]. Hypoalbuminaemia with low colloid

oncotic pressure and elevated pulmonary artery wedge pressure have been shown in people with acute systolic heart failure, which may facilitate the onset of pulmonary oedema[2].

CARDIAC PATHOLOGY

In dogs succumbing to babesiosis, myocardial necrosis, inflammatory infiltrate (which varied from round cells (macrophages and lymphocytes) only, round cells and neutrophils, and only neutrophils, haemorrhages and the presence of fibrin microthrombi was recently reported[11]. The lesions tended to be multifocal, but were generally limited to 1 area within the myocardium. The ventricles were the most commonly affected site, especially the left ventricle. Macroscopic cardiac lesions included pericardial effusion and pericardial, epicardial and endocardial haemorrhages.

In 1 study pericardial effusion was found to be the most common cardiac lesion in association with myocardial necrosis in dogs and cats[18]. Although the myocardial pathology in babesiosis can result in pericardial effusion; hypoalbuminaemia and increased capillary permeability are 2 other possible mechanisms of effusion in canine babesiosis[6,17,22,26].

Myocardial haemorrhages are seldom seen in dogs and if seen, are more common in the subepicardium[15]. Myocardial haemorrhages have been reported in hypoxia, acute infectious diseases[34], and disseminated intravascular coagulation (DIC)[32] all of which are part of the described pathogenesis of canine babesiosis[16]. Haemorrhages limited to the epi- or the endocardial surface of the heart can be an agonal change. However, this finding is relatively rare in the dog in comparison with horses and cattle[34] and may be indicative of a specific babesiosis-related lesion.

Myocardial necrosis is a common, nonspecific finding in systemic diseases, especially infectious and anaemic diseases. This necrosis is commonly diffuse[34], while in babesiosis it appears to be multifocal[6,11]. The presence of degeneration with inflammatory infiltrate but no fibroblasts, is consistent with acute necrosis of 12 hours to 4 days duration[34,47]. Myocardial necrosis can be a consequence of either coronary artery obstruction or inadequate oxygenation of the myocardial tissue[18]. Microthrombi, because of a hypercoagulable state due to DIC or IMHA[18], are relatively common obstructive lesions in the dog and cat. Endothelial injury is another cause of thrombosis[34] and is assumed to occur in babesiosis[31]. Hypoxia associated with shock can also cause myocardial necrosis[47]. All the conditions reported to be associated with myocardial necrosis, namely IMHA, DIC, brain involvement, hypoxia and shock, are reported complications of babesiosis[16]. In necrosis due to hypoxia and arteriosclerosis, the site reported is predominantly the subendocardium of the papillary muscles of both ventricles[14,47].

Inflammatory changes in the myocardium are relatively frequent in the dog[25]. They are commonly secondary to myocardial necrosis or systemic infectious disease[34], but are rarely considered as the primary disease[25]. The inflammatory infiltrate following necrosis is commonly neutrophilic[18]. Overwhelming inflammatory response was suggested as one of the mechanisms for tissue damage in canine babesiosis[32] and it may be responsible for part of the myocardial inflammation seen in this study.

RENAL EFFECTS

In the past, renal changes in babesiosis were attributed to haemoglobinuria and were referred to as haemoglobinuric nephropathy as babesiosis can result in a swollen kidney, dark in colour, with red-brown urine in the bladder. Microscopically the renal tubular epithelial (RTE) cells can be swollen and contain haemoglobin droplets and small vacuoles[26]. Proteinuria, RTE celluria, variable enzymuria, and azotaemia have been demonstrated in dogs with babesiosis[23]. However, these were all minimal changes and all could be consistent with hypoxia, reduced glomerular filtration rate (GFR), or reduced cardiac output. Renal haemodynamics are much more likely to be abnormal when cardiac dysfunction is present. Reduced renal blood flow and GFR rate are evidence of redistribution of blood flow that commonly occurs in early heart failure[7]. It is thus likely that the renal changes in canine babesiosis are secondary to cardiac dysfunction and that the cardiac complications are thus more important.

A recent study has shown that dogs with babesiosis tend to have lower serum sodium but there was no difference between mild, severe, or complicated cases of babesiosis[23]. In addition, dogs with babesiosis had a lower fractional clearance of sodium than clinically healthy control dogs, which can be interpreted as sodium retention by the kidneys. Children with malaria may show hyponatraemia, which is speculated to be associated with dehydration and inappropriate secretion of vasopressin (antidiuretic hormone)[13]. This sodium retention would also result in water retention, which will result in an expansion of the plasma volume. This finding has a bearing on the cardiac changes, as an increase in plasma volume will result in added strain on myocardial function.

PATHOPHYSIOLOGY

Babesiosis can result in various clinical manifestations that are difficult to relate to an organism that is solely restricted to the erythrocyte. This paper shows that homeostatic mechanisms of the body to the disease state could contribute to the cardiac and renal complications with the proposed pathophysiological being:

- By the parasites invading and replicating in the erythrocyte, babesiosis results in destruction of the erythrocyte with the development of anaemia and consequently hypoxia. The destruction of the erythrocyte is multi-factorial, including direct parasite damage to the erythrocyte membrane, splenic removal of damaged and parasitised erythrocytes, complement activation, and the presence of anti-erythrocyte antibodies, which result in a secondary IMHA.
- The kidneys are very susceptible to the effects of hypoxia as 20% of cardiac output goes through the kidney. The effect of hypoxia on the kidney is reduced GFR and tubular hypoxia. In addition dogs with babesiosis tend to be hypotensive, which will further reduce renal blood flow. The clinical manifestation of this would be pre-renal azotaemia (elevated urea/creatinine with high urine specific gravity).
- Tachycardia is a common clinical manifestation of babesiosis, which can be attributed to the anaemia, pyrexia, and acidotic state. During the cardiac cycle, tachycardia will result in a longer period of systole and a shorter period of diastole. As myocardial perfusion, via the coronary circulation, occurs during the diastolic period, a shorter diastolic period will result in reduced coronary artery blood flow with compromised myocardial perfusion. The net result is myocardial hypoxia.
- Another effect of the tachycardia is that the heart is forced to work at a faster rate with a reduced oxygen supply, the latter by a combination of reduced coronary circulation and less oxygen in the blood because of the anaemia. Dogs with babesiosis not only have less haemoglobin but the remaining haemoglobin has been shown to be sub-functional[43], which will further contribute to the hypoxic state and thus myocardial hypoxia.
- Prolonged myocardial hypoxia will result in myocardial depression, which in turn can result in hypotension. Hypotension will further reduce coronary circulation, thus aggravating the

myocardial hypoxia.

- Dogs with babesiosis have pathological changes within the myocardium (myocardial necrosis, inflammation, haemorrhage, fibrin microthrombi) that are usually in the left ventricle, which has the highest metabolic requirement. These changes may be due to an inflammatory reaction to the pavementing of parasitised cells against the endothelium *via* adhesion molecules, coagulopathy, or from myocardial hypoxia.

THERAPEUTIC RECOMMENDATIONS

To improve the management of canine babesiosis, especially complicated cases, the following therapeutic/monitoring recommendations are advocated:

- **Cardiac pathology**

Taking cognisance that myocardial lesions may be more common than previously thought which can result in hypotension, intravascular fluid overload and pulmonary oedema, necessitating the careful use of intravenous fluids as well assessing the patient for the presence of myocardial pathology by measuring serum troponins. Additional therapy that may be required would be arrhythmia control, positive inotropic support, strict cage rest, oxygen supplementation, and diuretics.

- **Serum sodium**

Monitoring of serum sodium and utilising fluids to maintain and/or correct hyponatraemia.

- **Serum albumin**

Monitoring serum albumin and replacing with fresh plasma and/or synthetic colloids, if necessary.

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