Diagnostic and therapeutic studies on dilated cardiomyopathy in Doberman Pinschers

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Summary

Cardiac diseases are spread in human populations. Although inherited forms of these diseases are relatively rare in human, they are very frequent in dog and cat (between 10% to 50%). Dilated cardiomyopathy (DCM) is the focus of our research activity, with several aims:

- Establish new methods for earlier and better recognition of the disease
- Perform therapeutic studies
- Obtain genetic markers by identifying disease-associated locus in genome and causative mutation in involved genes
- Reinforce the knowledge base of homologous human inherited disease useful for developing in the future animal models that could be used for therapeutic strategies.
- To establish cohorts of well clinically characterized individuals, with affected and healthy animals. More efficient samples recruitment with several centers distributed in Europe.
- To develop a DNA library of large panels of dogs, with relevant clinical history

Research Objectives

Dilated cardiomyopathy (DCM) is a well-known and common cause of congestive heart failure and sudden death in dogs that resembles dilated cardiomyopathy in humans and other species. This disorder is characterized by dilatation of the four cardiac chambers, caused by biventricular systolic dysfunction (hypkinesia) in the absence of other identifiable systemic disorder or cardiovascular disease. The thinning of the myocardium lowers the myocardial contractility. The cardiac flow decreases and a cardiac insufficiency is resulting. The reduced systolic function leads to the development of congestive heart failure, i.e. pulmonary congestion, edema, and ascites. Arrythmia is also common in diseased individuals, particularly atrial fibrillation and ventricular ectopies. Syncopes or sudden death may precede signs of congestive heart failure.

In the Doberman Pinscher, DCM is characterized by frequent and often severe ventricular arrhythmias and is clinically distinct from other canine dilated cardiomyopathies in that the arrhythmias appear often many years before the hearts will show the typical myocardial failure with a systolic dysfunction. Sudden death occurs as the first clinical sign of DCM in about 30% of all Doberman Pinschers destined to develop DCM with systolic dysfunction. Doberman Pinschers have a subclinical period, usually between 2 and 4 years, during which they may or may not have echocardiographically detectable myocardial failure but no clinical signs. Whereas they may have a normal echocardiographic examination, they usually show electrical abnormalities in their 24-hour ECG examination. Therefore, a 24-hours ECG is considered the best diagnostic test for early recognition of the disease. In some dogs the disease stabilizes for several years. Although it appears that males and females are equally affected, more males develop heart failure and males die earlier of their disease than do females. Approximately 75% are between 5 and 10 years of age at the time of death. Once clinical symptoms appear, the course of the disease in Doberman

Pinschers is progressive and severe leading to death or euthanasia within 3 - 6 months after appearance of the first clinical symptoms. Compared to other canine cardiomyopathies Doberman cardiomyopathy has an early age of onset (subclinical stage) and a very distinct clinical phenotype, which makes it well suited for a molecular analysis. Given the distinct clinical phenotype of Doberman cardiomyopathy it is likely that this phenotype is caused by a specific mutation, which is not involved in other forms of canine dilated cardiomyopathy.
In human population, DCM has a prevalence of one case out of 2500 individuals with an incidence of 7/100,000/year. The long-term prognosis is considered poor, varying from 52-77% surviving the first year after diagnosis. However, DCM is probably under diagnosed and is now believed to account for a much larger number of cases, owing to the fact that subjects may remain asymptomatic until marked ventricular dysfunction has occurred. More recent studies support that familial dilated cardiomyopathy (FDC) may account for between 35% and 48% of seemingly familial DCM.
Candidate gene screening and linkage analyses in large families were successful in identifying 24 disease genes. Currently, genetic tests are available for a small subset of these genes and there appear to be more yet undetected gene abnormalities. It is very difficult to diagnose the disease because it can be only recognized after the development of the first clinical symptoms. It frequently happens that a dilated cardiomyopathy is diagnosed only at a late stage. DCM is usually detected by signs of heart failure, such as shortness of breath, swelling of the ankles and legs, and fatigue, or sudden death.
There is currently no good animal model for human DCM. These tools and the physiopathological proximity with human allow to think that the dog is a good model to simplify the heterogeneity of the human DCM. The interest of the each presented model resides in the fact that canine breed may be considered as a genetic isolate and could correspond as many different models for Human. The identification of the genes implied in the cardiac function and its regulation is a preamble with the understanding of their role and their interaction in cardiac physio(patho)logy. Then, knowing the specific cardiac structures and the pathophysiology in an animal model can help in the search for new drug targets and drug development in humans.

Key Findings

Over the last years we focused our research in further building up our cohort of privately-owned Doberman Pinschers in a long-term follow-up study. More than 5000 examinations have been performed over the last 15 years and the study is still ongoing. This study design enabled us to see the dogs on a yearly base and built up a blood/DNA bank which includes dogs in different stages of the disease. As many patients came initially as apparently healthy, we have also samples from times before the disease became apparent on echocardiography or Holter examination. This was used to establish several biomarkers (NT-proBNP, cTNI) and new echocardiographic parameters (Simpson Method of disc, EPSS, Strain measurements) as early diagnostic markers. Some of them are now considered to be new gold standards to diagnose DCM in DP (Wess et al., 2017). An important study was also the evaluation of risk factors to die from sudden cardiac death, as there were so far not any comparable studies available in veterinary medicine. The main result was, that a dilated heart with poor contractility is the biggest risk factor, followed by fast ventricular premature contraction. Furthermore, we were able to establish the DP as a new model for DCM in humans (Wess et al., 2019).
The aptamer BC 007 was developed for the neutralization of functional autoantibodies such as those against β1-adrenergic receptor (β1-AAB), which are highly frequent in patients with dilated cardiomyopathy (DCM), and are being increasingly accepted as disease drivers.
Using Doberman Pinschers (DP), which frequently develop DCM associated with β1-AAB positivity,(Wess et al., 2019) the safety and efficacy of BC 007 for β1-AAB neutralization and the DP outcomes were studied. Together with “Berlin Cures”, a human startup company we performed a treatment study with BC 007 for β1-AAB neutralization and showed that it was safe, resulted in a long-lasting reduction of β1-AAB and prolonged the survival of DP with DCM (Werner et al., 2020).
Currently we are also cooperating with Prof. Lohi form the University of Helsinki in a multicenter study on establishing a new genetic locus of DCM in DP using a genome wide association study.

A new locus was found and now we are testing this new detected mutation in a cohort of human patients with DCM. The results of that study are promising, and the manuscript is under preparation. Additionally, several other treatment and diagnostic studies are currently under investigation.

Selected publications

1. Werner S, Wallukat G, Becker NP, et al. The aptamer BC 007 for treatment of dilated cardiomyopathy: evaluation in Doberman Pinschers of efficacy and outcomes. ESC Heart Fail 2020.
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5. Kluser L, Maier ET, Wess G. Evaluation of a high-sensitivity cardiac troponin I assay compared to a first-generation cardiac troponin I assay in Doberman Pinschers with and without dilated cardiomyopathy. J Vet Intern Med 2019; 33: 54-63.
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10. Beier P, Reese S, Holler PJ, et al. The role of hypothyroidism in the etiology and progression of dilated cardiomyopathy in Doberman Pinschers. J Vet Intern Med 2015; 29: 141-149.

Funding

Funder	Project title	Start date	End date
Pharmaceutical company	Evaluation of a sartan drug in feline hypertrophic cardiomyopathy	2020	2022
DFG	Grossgeräteantrag Herzultraschall	2018	2018