Genotype-Phenotype Associations in Arrhythmogenic Right Ventricular Cardiomyopathy, with a Focus on the Arrhythmic Risk

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Background

Humans

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder characterized by disruption of the myocytic architecture resulting in electrical instability and increased risk of life-threatening ventricular arrhythmias (1).

Risk of sudden cardiac death and recurrent arrhythmia

Although the overall risk of sudden cardiac death (SCD) is low (2), ARVC has been reported to be an important cause of SCD in adults younger than 35 years, accounting for up to 11% of SCD cases (3–5) and with up to 30% in athletes (6–8).

The 2006 ACC/AHA/ESC guidelines recommend the use of an ICD in patients with ARVC and documented VT or VF (9). Risk stratification overall remains imperfect, as has recently been underlined by the Task Force Consensus Statement on Treatment (10). To date, there is only retrospective data from small cohorts available. Both definition of outcome and selection of patients vary highly in the named studies.

Defibrillation safety margin testing

ICDs were introduced as a therapy for ARVC patients in the mid 1990s (11). At the time it was felt necessary to prove the functionality of the device by formally testing sensing and conversion efficacy of ventricular fibrillation (12). With the increasing reliability of ICD systems and clincial implant experience, the necessity of formal defibrillation threshold testing (DFT) has been questioned (13–16). Recent randomised studies have indicated the risk to benefit-ratio is in favour of omitting DFT testing during ICD implantation (17,18). However, no patients with ARVC were included in either of these studies. Previous studies on DFT testing have not formally studied ARVC patients, who are likely to be underrepresented (15,19–21), either including a a handful of cases (16,22) or excluding them (17). A small report on 12 patients with ARVC stated that they had similar defibrillation thresholds as non-ARVC patients, however, in a third of the patients multiple endocardial positions needed to be tested in order to find appropriate sensing and defibrillation thresholds (23).

Heart failure

Heart failure (HF) is a rare, but important outcome for patients with ARVC. In a large cohort of patients with definite ARVC, the incidence of HF was reported 13%, with 4% of patients proceeding to heart transplantation (HTx) (2). Another study reported death due to chronic HF in 11% of patients, with the age at onset being significantly higher than in patients presenting with arrhythmia (24). In a cohort of patients carrying an ARVC-associated gene mutation, the incidence of HF has been reported at 5% (25). Patients with multiple mutations are thought to develop a more severe

phenotype (25–27) and patients with a desmoplakin (DSP) mutation to more likely develop HF (25).

Boxer dogs

A disease similar to the one known in humans was described in Boxer dogs by Harpster in 1983 (28). He reported a disease, which unlike cardiomyopathies in other large dogs, was lacking ventricular dilation and atrial fibrillation but was distinguished by extensive histological myocardial alterations including fibrofatty replacement of myocardial cells. He suggested that ventricular premature complexes (VPC) were a pathognomonic sign and documented frequent ventricular tachycardia in affected dogs. He divided affected dogs into three categories: Category 1.) Asymptomatic dogs with ventricular arrhythmias; category 2.) Dogs with syncope or weakness and ventricular arrhythmias; category 3.) Congestive heart failure in association with ventricular arrhythmias (28).
Subsequent research focused on the arrhythmogenic risk as well as on the genetic causes of the disease in Boxer dogs (29–37). It was recognised that Boxer dogs might serve as a naturally occurring model for the human disease, based on the close clinical and pathological resemblances of the canine to the human disease (38). However, there are no consensus diagnostic criteria for ARVC in Boxer dogs leading to a discrepancy of diagnostic criteria between the different studies. The aforementioned issue prevents direct comparison between the studies.

Aims

Humans

Risk of sudden cardiac death and recurrent arrhythmia

We aimed to identify clinically applicable, non-invasive predictors for arrhythmic risk in ARVC and to combine detected predictors into a clinically useful risk score.

Defibrillation safety margin testing

Our objective was to study the outcome of defibrillation safety margin (DSM) testing in patients with ARVC.

Heart failure

We aimed to define the genotype and disease progression of patients with heart transplantation or death due to heart failure with ARVC.

Boxer dogs

Our objective was to develop diagnostic criteria for ARVC in Boxer dogs, which can be easily applied to clinical practice and do not rely solely on the number of VPCs in a single 24h-ECG, in order to standardise disease classification. We anticipate that a more uniform and consistent clinical definition of the canine phenotype will allow direct comparison with the

human phenotype and hence ultimately improve understanding of the condition.

Methods

Humans

Patients referred to the Inherited Cardiovascular Disease Unit at The Heart Hospital in London, and to St Georges Hospital, London (before 2003), with a suspicion of ARVC, or with a premature SCD and/or known ARVC in the family (with the initial family member not checked at our hospitals), and who had received genetic testing, were recruited consecutively. Only patients who fulfilled diagnostic criteria according to the 2010 task force criteria (1) at any time throughout the course of their disease were included for the development of the score. Family members were excluded; therefore, all patients were unrelated.

Detailed clinical and genetic data was collected at baseline and during follow up.

Clinical evaluation included personal and family history, 12-lead-electrocardiogram (ECG), signal averaged ECG (SAECG) and 24h-ECG, 2D-echocardiography, and cardiopulmonary exercise test (CPEX).

Follow up visits were performed as clinically necessary, usually every 6-12 months. Patients who had not been seen for at least 2 years were contacted by telephone in January 2015 using a structured questionnaire.

Paper prints of the ECGs were evaluated with regard to electrical axis, QRS duration in leads V1 and V6, duration of terminal activation measured from the nadir of the S wave to the end of the QRS in leads V1 and V2, presence of T wave inversions in all leads, presence of Q waves in all leads, presence of low voltage, presence of delayed R progression, presence of left or right bundle branch block, presence and configuration of ventricular ectopics.

Automated interpretation of SAECGs was analyzed with regard to filtered QRS duration (fQRSd), duration of the terminal QRS, low-amplitude signal duration (LAS), root-mean-square voltage of the terminal 40 ms (RMS), the same parameters in only the Z axis, the number of beats analysed and the documented noise. SAECGs with a noise $\geq$ 0.5 mV were excluded.

Automated interpretation of 24h-ECGs was utilised for the number of ventricular ectopics, couplets, triplets, tachycardias and supraventricular ectopics and tachycardias and prevalence of atrial fibrillation. Full disclosure was available if needed.

CPEX was performed using a standard Bruce protocol. Maximal oxygen consumption (VO2max), its percentage of predicted, peak heart rate, its percentage of predicted, respiratory quotient, minutes of exercise (always rounded down to the next lower), achieved power in Watts, occurring arrhythmias and current medication were taken from the standardised reports.

All echocardiographic measurements were taken from the standardised reports. Information on decreased RV function, dilatation and wall motion abnormalities were also taken from the written reports, unless there were

conflicting reports, in which case three cardiologists with a special interest in cardiomyopathies reviewed the images independently. A consensus was arrived at.
Genotyping was performed using next generation sequencing as described before (39).

Boxer dogs

All Boxer dogs admitted to the cardiology service of The Royal Veterinary College between 2001 and 2013 were included. The reason for referral, clinical signs, symptoms and medications were obtained from veterinary medical records. 24h-ECGs and echocardiograms were analysed retrospectively.
24h-ECGs were analysed for the number of ventricular premature complexes (VPC), couplets, triplets, and episodes of ventricular tachycardia (VT). The morphology of VPC, couplets, triplets and VTs were evaluated and defined as monomorphic or polymorphic. Monomorphic VPC had the same visual vector. Polymorphic VPC had >1 vector. The most commonly appearing morphology was used to describe the overall vector. The duration and rate of supraventricular and ventricular arrhythmias was recorded. Couplets, triplets and VTs were defined as polymorphic if they displayed different morphologies within their single beats. R-on-T phenomenon was defined as a VPC superimposed on the T wave as postulated from other sinus beats (40). 24h-ECGs were excluded if the printout quality was sub-optimal for analysis.
Left ventricular end-diastolic (LVIDd) and end systolic (LVIDs) diameter were measured in echocardiograms in the parasternal long-axis view using 2D images. Ejection fraction was calculated using the Simpson's method of disks (41).
Dilated cardiomyopathy (DCM) was defined by LVIDd > 5.18 cm, LVIDs > 3.63 cm and FS < 23% which are the 95th and 5th percentiles in normal boxers, respectively (42). The presence of aortic stenosis (AS) was determined using standard Doppler assessment of AV flow. Aortic stenosis was defined by a AV max velocity ≥ 2.25 m/s (43). Diastolic function was assessed by mitral inflow pattern using PW-Doppler (44). RVOT size was measured at end-diastole in the parasternal short axis, from the anterior RV wall to the aortic valve (41). RV function, dilatation and wall motion abnormalities were estimated visually by one investigator, blinded to the number of VPC, and categorised as mild, moderate and severe.

Main results

Humans

Risk of sudden cardiac death and recurrent arrhythmia: Risk score

Patients with a suspicion of ARVC or family history of ARVC/Sudden cardiac death who underwent genetic testing and fulfilled the 2010 task force criteria were consecutively recruited. Detailed clinical data were collected at baseline and during follow up. Clinical endpoint was a

composite of recurrent sustained ventricular arrhythmias and hospitalization due to arrhythmias. Multivariable logistic regression was used to develop models to predict the arrhythmic risk.
Results: One hundred and thirty five patients were included of whom 35 patients (31.9%) reached the endpoint. Univariable analysis showed significant differences in 12 lead, signal averaged and 24h-ECG, cardiopulmonary exercise test and 2D-echocardiogram compared to those who did not reach the endpoint. A model consisting of filtered QRS duration, nonsustained VT (NSVT) on 24h-ECG and absence of negative T waves in lead aVR was able to predict arrhythmic events with a sensitivity of 81.8%, specificity of 84.0% and negative predictive value of 95.5% at an early stage of the disease.
Conclusion: A risk score consisting of filtered QRS duration ≥117ms, presence of NSVT ≥3 beats in a 24h-ECG and absence of negative T waves in lead aVR was able to predict arrhythmic events.

Heart Failure in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Genetic and Clinical Characteristics.

Patients with a definite diagnosis of ARVC who underwent genetic testing were consecutively recruited. Detailed clinical data was collected at baseline and during follow up. Clinical endpoint was a composite of death due to HF and heart transplantation. 135 patients were included. 8 (5.9%) patients reached the end point. The great majority of HF patients carried a Plakophilin 2 mutation. 50% had multiple mutations. They had more T wave inversions, abnormal signal averaged electrocardiograms, and RV dilatation and dysfunction than patients without HF.
Conclusion: HF occurred in about 6% of patients with a definite diagnosis of ARVC. Patients with HF predominantly carried Plakophilin 2 mutations and often had multiple mutations.

ICD defibrillation safety margin testing in patients with arrhythmogenic right ventricular cardiomyopathy

ARVC patients of a tertiary referral centre with ARVC who have been genetically tested and implanted with an ICD were consecutively recruited. Reports were scrutinised for information on ICD implantation, DSM testing, outcome of the DSM testing. Adequate DSM was defined as 1 successful shock at 14 J or 2 shocks of 10 J below maximal output.
Results: 122 patients with definite, borderline or possible ARVC were implanted with an ICD. Overall, 47 DSM tests at implant and 20 DSM test during generator replacement were performed. 4 DSM (6.0%) were labelled as inadequate and led to system modifications. All these patients were male and had a family history of ARVC. They were significantly younger than their counterparts with acceptable DSM (24.5±10.0 vs. 40.8 ±11.9, p 0.011). They showed a more advanced stage of their disease. Half of them had potentially pathogenic variants or variants or variants of unknown significance in desmosomal genes.
Conclusion: 6% of DSM tests at ICD implantation or generator replacement in patients with ARVC were initially unable to cardiovert the induced

arrhythmia. Patients with more advanced stages of the disease appeared to be at higher risk for inadequate DSM.

Boxer Dogs

The phenotype of arrhythmogenic cardiomyopathy in Boxer dogs

Clinical records from 264 Boxer dogs from a referral veterinary hospital were retrospectively analysed. ARVC was initially diagnosed according to the number of ventricular premature complexes (VPC) in the 24-hour-Holter-ECG in the absence of another obvious cause. Dogs diagnosed in this fashion had more VPC, syncope, more polymorphic VPC, couplets, triplets, VTs and R-on-T phenomenon, decreased right ventricular function and dilatation in comparison to a control group of all other Boxer dogs seen by the Cardiology Service over the same period. Presence of couplets and R-on-T phenomenon on a 24h-ECG were identified as independent predictors of the diagnosis. A diagnosis based on ≥100 VPC in 24 hours, presence of couplets and R-on-T phenomenon on a 24h-ECG was able to select Boxer dogs with a phenotype most similar to human ARVC.

We suggest the diagnosis of ARVC in Boxer dogs requires two out of the three following criteria: presence of ≥ 100 VPC, presence of couplets or R-on-T phenomenon on a 24 h-ECG.

Publications

The following publications are submitted or near submission

Humans

- Vischer AS, Castelletti S, Syrris P, Kadoglou N, Denhaerynck K, Bastiaenen R, Behr ER, McKenna WJ, Jacoby D, Pantazis A: Risk score for early prediction of arrhythmic events in arrhythmogenic right ventricular cardiomyopathy based on long term follow up.
- Vischer AS, Castelletti S, Syrris P, McKenna WJ, Pantazis A: Heart Failure in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Genetic and Clinical Characteristics.
- Vischer AS, Castelletti S, Syrris P, Lambiase P, McKenna WJ, Pantazis A: ICD defibrillation safety margin testing in patients with arrhythmogenic right ventricular cardiomyopathy.
- Castelletti S, Vischer AS, Bastiaenen R, Syrris P, Jenkins S, Behr ER, McKennaWJ, Pantazis A: Disease expression and outcome of pregnancy in ARVC.
- Castelletti S, Vischer AS, Syrris P, Crotti L, Ghidoni A, Parati G, Jenkins S, Kotta M-C, McKenna WJ, Schwartz PJ, Pantazis A: Genotype-phenotype Correlation in Arrhythmogenic Right Ventricular Cardiomyopathy Caused by Desmoplakin Missense and non-Missense Mutations

Boxer dogs

- Vischer AS, Connolly DJ, Coats CJ, Luis Fuentes V, McKenna WJ, Castelletti S, Pantazis A: The phenotype of arrhythmogenic cardiomyopathy in Boxer dogs: get the diagnosis right.

Published Reviews

- Vischer AS, Pantazis A: Anderson-Fabry Disease: What is the Problem and how does this translate into clinical signs. E-Journal of Cardiology Practice. 2016;14(6)
- Pantazis A, Vischer AS, Perez-Tome MC, Castelletti S: Diagnosis and management of hypertrophic cardiomyopathy. Echo Res Pract. 2015;2(1):R45-R53

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