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Review

Can preload-reducing therapy prevent disease progression in arrhythmogenic right ventricular cardiomyopathy? Experimental evidence and concept for a clinical trial

Larissa Fabritz [a,b,*], Lisa Fortmüller [b], Ting Y. Yu [a,c], Matthias Paul [b], Paulus Kirchhof [a,b]

[a] Centre for Cardiovascular Sciences, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, United Kingdom
[b] Department of Cardiology and Angiology, University Hospital Münster, Germany
[c] Physical Sciences of Imaging in the Biomedical Sciences, Doctoral Training Centre, School of Chemistry, University of Birmingham, United Kingdom

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy and a leading cause of sudden cardiac death in a young population. ARVC is especially common in young athletes. Mutations in different desmosomal genes have been identified causing dysfunctional cell–cell contacts. Reduced myocardial expression of plakoglobin in cell–cell contact complexes appears to associate with disease manifestation in patients harbouring mutations within other cell–cell contact genes. Experimental data suggest that preload reduction may be a simple and effective intervention to prevent disease progression and ventricular arrhythmias in ARVC. This review discusses the potential effects of this innovative approach and describes the design of the first controlled trial of preload-reducing therapy in patients with ARVC.

Contents

1. The medical problem

Arrhythmogenic right ventricular cardiomyopathy (ARVC) alongside hypertrophic cardiomyopathy (Kaltman et al., 2011), is one of the leading causes of sudden death in the Young, and one of the main causes of unexpected death in athletes (Corrado et al., 2006; Marcus et al., 2010). The prevalence of ARVC is estimated at 1:1000 in Europe (Sen-Chowdhry et al., 2010). Every year, at least one

* Corresponding author. Centre for Cardiovascular Sciences, School of Clinical and Experimental Medicine and SWBH NHS Trust, College of Medical and Dental Sciences, University of Birmingham, Wolfson Drive, Edgbaston Birmingham B15 2TT, UK. Tel.: +44 121 414 6259, +44 121 414 6938; fax: +44 121 414 8867.
E-mail address: L.Fabritz@bham.ac.uk (L. Fabritz).

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professional cyclist, football/soccer or basketball player makes headline news due to sudden cardiac death during a race or a match secondary to ARVC. Practice of competitive sports clearly co-segregates with ARVC, suggesting that strong physical training, and especially endurance sports such as cycling, swimming or long-distance running, accelerates disease development in patients (Corrado et al., 2006; Heidbuchel et al., 2003).

2. Evidence of disease mechanism

In the majority of patients with ARVC, mutations in genes encoding proteins of mechanical intercellular connections have been identified, leading to the recognition of ARVC as a "disease of the desmosome" (Asimaki et al., 2007; Gerull et al., 2004; Sen-Chowdhry et al., 2007; Syrris et al., 2007; van Tintelen et al., 2006). Among those with predominant autosomal-dominant mode of inheritance (Sen-Chowdhry et al., 2010) are plakophilin, desmoplakin, desmoglein, desmocollin, and plakoglobin. Mutations within plakophilin-2 were the first to be identified in a considerably large proportion of patients with ARVC (Gerull et al., 2004; van Tintelen et al., 2006), however, penetrance and clinical disease manifestation were variable (Dalal et al., 2006; Lahtinen et al., 2011) outside of specific, often recessive subforms such as Naxos disease or Carvajal syndrome (Norgett et al., 2000; Protonotarios et al., 2001).

Recent reports suggest that desmoglein-2 mutations harbour dual effects by: a) modifying the interaction with n-cadherin at the myocardial cell–cell contacts, thereby possibly reducing plakoglobin binding to the cell–cell contact complexes (Gehmlich et al., 2010; Syrris et al., 2007), and b) inducing cardiomyocyte necrosis and cardiac fibrosis (Kant et al., 2012; Pilichou et al., 2009). Similarly, both electrophysiological alterations (e.g. conduction slowing), and structural changes (i.e. fibrofatty replacement) are found (Gomes et al., 2012). Of note, the electrophysiological changes precede structural alterations in desmoplakin mutants (Gomes et al., 2012).

Analyses of right ventricular endomyocardial biopsies and cardiac post-mortem specimen from ARVC patients carrying different desmosomal gene defects identified reduced plakoglobin expression (Asimaki et al., 2009) thereby indicating that a reduction of this desmosomal protein could pathophysiologically be regarded as the "final common pathway" in ARVC and may also be utilized to discriminate ARVC from other cardiomyopathies (Asimaki et al., 2011).

3. Evidence from disease models

Several elegant studies in genetically modified mice have shown that genetic disruption of desmoplakin, plakoglobin, and desmoglein is sufficient to replicate the phenotype of ARVC (Garcia-Gras et al., 2006; Gehmlich et al., 2011; Kirchhof et al., 2006; Krusche et al., 2011; Pilichou et al., 2009). Disease expression differs in models carrying different genetic defects: right ventricular dysfunction and ventricular arrhythmias are predominantly observed in plakoglobin-deficient mice (Kirchhof et al., 2006); biventricular fibrosis is most prominently detected in desmoplakin-deficient mice (Garcia-Gras et al., 2006); and cardiomyocyte necrosis/fibrosis are found in desmoglein-mutant mice (Krusche et al., 2011; Pilichou et al., 2009).

More recent data confirm that cardiomyocyte-directed deletion of plakoglobin (i.e. >80% reduction of plakoglobin expression by induced heart-directed deletion) causes the histological changes of ARVC including fibrosis and heart failure (Li et al., 2011), while heterozygous deletion of plakoglobin (i.e. reducing plakoglobin content to approximately 50%) provokes the complete functional phenotype of ARVC without histological alterations (Kirchhof et al., 2006). Consequently, it could be hypothesised that lack of plakoglobin at the mechanical cell–cell contacts is responsible for the functional changes in ARVC, including right ventricular enlargement, right ventricular dysfunction, and right ventricular conduction slowing, while dislocation of plakoglobin to the nuclear compartment in the cell, e.g. secondary to decreased plakoglobin binding at the cell membrane, may confer some of the structural changes which are summarised as fibro-fatty infiltration (Garcia-Gras et al., 2006), and may be the late reflection of cardiomyocyte necrosis (Pilichou et al., 2009).

This might also explain the sequence of changes associated with desmoglein mutants whereby functional electrophysiological changes precede structural alterations (Gomes et al., 2012).

To summarise, the different models support a cascade of events by which a genetically conferred reduction of plakoglobin in the intercellular connections results in "early" functional defects such as ventricular arrhythmias and right heart dilation, while a more marked reduction of plakoglobin and/or a translocation of plakoglobin to the nucleus appears to be associated with the later development of fibrosis, cardiomyocyte necrosis and other structural changes induced by mutated cell–cell contact proteins.

In the plakoglobin-deficient model, endurance exercise training markedly accelerates the development of ARVC (Kirchhof et al., 2006), thereby corroborating the clinical suspicion that chronically increased right ventricular preload as provoked by endurance sports expedites disease progression (Corrado et al., 2006; Heidbuchel et al., 2003). Of note, athletes with right ventricular arrhythmias show reduced right ventricular function when compared to athletes without arrhythmias (Ector et al., 2007). Even in otherwise healthy endurance athletes, intense exercise has recently been shown to cause transient right ventricular dysfunction and structural remodelling in magnetic resonance imaging (La Gerche et al., 2012).

4. The need for a disease-modifying therapy in ARVC

At present, no therapy is available to prevent disease progression in ARVC patients. Management, therefore, focuses on reducing the risk of sudden death by antiarrhythmic drug therapy, implantation of a defibrillator, catheter ablation to prevent frequent arrhythmia recurrences, or a combination of these (Sen-Chowdhry et al., 2010; Wichter et al., 2004). Antiarrhythmic drug therapy is needed in addition to defibrillator therapy in many ARVC patients to reduce the burden of ventricular arrhythmias (Marcus et al., 2009; Wichter et al., 2004), and catheter ablation of ventricular tachycardias is performed regularly as palliation in patients with frequent shocks (Carbucicchio et al., 2008). Although the use of 3D-electroanatomic mapping systems and epicardial ablation strategies are associated with longer VT-free survival, recurrence rates remain considerable (Philips et al., 2012). Furthermore, many patients, though not eligible for defibrillator implantation, are still at increased risk of sudden death (Corrado et al., 2010). Complications associated with defibrillator therapy are higher in ARVC patients due to the diffuse or segmental progressive right ventricular fibro-fatty replacement of viable myocardium (Marcus et al., 2009; Wichter et al., 2004). Antiarrhythmic therapy also harbours specific therapy-associated problems: 1. Antiarrhythmic drug therapy is still widely empiric and often relies on sotalol and amiodarone, two agents with well-known cardiac and extracardiac toxicity (Marcus et al., 2009). 2. Even when managed in specialised centres with diligent intra- and perioperative management of implantable cardioverter-defibrillator (ICD) recipients, frequent defibrillator-related complications (affecting up to 45% of patients during long-term follow-up; (Tavernier et al., 2001; Wichter et al., 2004)) and a high prevalence of adequate defibrillator shocks due to disease progression are still unresolved clinical problems in this cohort of relatively young, active, and otherwise healthy individuals. Furthermore, the