

# Traditional vs. genetic pathogenesis of arrhythmogenic right ventricular cardiomyopathy

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Arrhythmogenic right ventricular cardiomyopathy (ARVC), a predominantly familial and autosomal dominant inherited heart muscle disorder, is pathologically characterized by progressive right ventricular myocardial atrophy and fibrofatty replacement and clinically by ventricular arrhythmias with left bundle branch block morphology. Symptoms poorly reflect disease severity, with disease commonly first manifesting as sudden death among the young. The inflammatory and apoptotic theories first put forth to explain ARVC pathogenesis do not explain all cases, and advances in genetic technology have allowed to elucidate genetic mechanisms, with desmosomal mutations attracting much attention. As reviewed here, various non-mutually exclusive pathogenetic mechanisms therefore appear to underlie ARVC.

## Keywords

Arrhythmogenic right ventricular cardiomyopathy • Pathogenesis • Inflammation • Apoptosis • Gene • Desmosome

## Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) has been characterized as a predominantly autosomal dominant inherited disease, affecting ~1 in 5000 individuals in the overall population.<sup>1,2</sup> Arrhythmogenic right ventricular cardiomyopathy also includes Naxos Disease and Carvajal Syndrome, two specific autosomal recessive inherited diseases, with 50% of ARVC cases being familial.<sup>3</sup> Typical pathological features of ARVC include cardiomyocyte atrophy and fibrofatty replacement, which as the disease name reflects, were initially thought to be restricted to the right ventricle (RV), mostly involving the inflow tract, outflow tract, or apex, the so-called ‘triangle of dysplasia’<sup>4,5</sup>; however, left ventricular (LV) involvement has been documented in some of cases.<sup>6</sup> Clinically, ARVC most often presents with ventricular arrhythmias, typically ventricular tachycardia (VT) with left bundle branch block morphology. Young individuals and athletes are at high risk; sudden cardiac death might occur during exertion, which appears not only to be a trigger but also contribute to disease progression,<sup>7</sup> thus, recommendations of appropriate physical activities for individuals with ARVC were established.<sup>8</sup>

Arrhythmogenic right ventricular cardiomyopathy’s fatal severity has fuelled research into underlying mechanisms. The inflammatory and apoptotic theories, first proposed based on histopathological detection of inflammation and apoptosis, did not explain all disease

cases. Advances in genetic technology have revealed 13 genes associated with ARVC<sup>9</sup> (Table 1), and 5 are in genes encoding desmosomal proteins, including those for plakoglobin (*JUP*), desmoplakin (*DSP*), plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*), and desmocollin-2 (*DSC2*) (Figure 1). The desmosome plays a critical role in maintaining stable intercellular junctions and its alteration may underlie ARVC, which has also been coined ‘desmosomal cardiomyopathy’.<sup>24</sup> Despite the aforementioned findings, a consensus on the etiopathogenesis of ARVC remains elusive, and this review presents the evolution in its understanding.

## Inflammatory theory

Several case reports have described patients with clinical presentation compatible with ARVC and histopathological findings consistent with myocarditis, suggesting a potential causal association between myocarditis and ARVC.<sup>24–30</sup> The inflammatory theory was therefore proposed and corresponding infective mechanisms hypothesized to be responsible for the onset and progression of ARVC. To this end, various cardiotropic viruses, such as enteroviruses, cytomegalovirus, parvovirus, hepatitis C virus, and adenovirus, have been detected in sporadic ARVC.<sup>31</sup> Enteroviruses were first investigated in ARVC, and Matsumori and Kawai<sup>32</sup> established an experimental model in which BALB/C mice infected with coxsackievirus B3 showed selective right ventricular myocardial

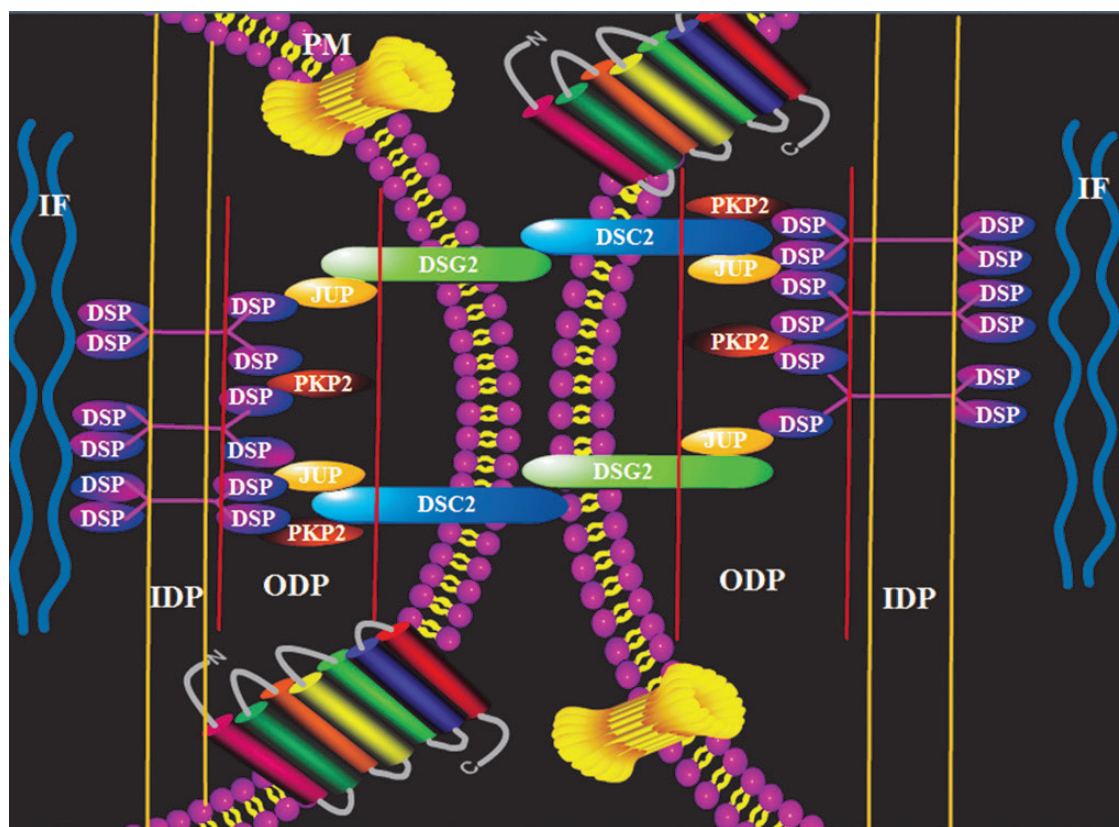
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**Table 1** Mapped chromosomal loci and causal genes for ARVC

Gene	Protein	Loci	Mode	Type	References
<i>TGFβ-3</i>	TGFβ-3	14q23-q24	AD	ARVC1	10
<i>RyR2</i>	RyR2	1q42-q43	AD	ARVC2	11
<i>TMEM43</i>	TMEM43	3p23	AD	ARVC5	12
<i>DSP</i>	DSP	6p24	AD/AR	ARVC8	13
<i>PKP2</i>	PKP2	12p11	AD	ARVC9	14
<i>DSG2</i>	DSG2	18q12	AD	ARVC10	15
<i>DSC2</i>	DSC2	18q12	AD	ARVC11	16
<i>JUP</i>	JUP	17q21	AR	ARVC12	17
<i>DES</i>	DES	2q35	AD	–	18
<i>TTN</i>	TTN	2q31.2	AD	–	19
<i>LMNA</i>	LMNA	1q22	AD	–	20
<i>PLN</i>	PLN	6q22.1	AD	–	21
<i>CTNNA3</i>	CTNNA3	10q21.3	AD	–	22

TGFβ-3, transforming growth factor beta-3; RyR2, cardiac ryanadine receptor 2; TMEM43, transmembrane protein 43; DSP, desmoplakin; PKP2, plakophilin-2; DSG2, desmoglein-2; DSC2, desmocollin-2; JUP, plakoglobin; DES, desmin; CTNNA3, αT-catenin; LMNA, lamin A/C; PLN, phospholamban; TTN, titin; AD, autosomal dominant; AR, autosomal recessive. Desmoplakin autosomal recessive mutation leads to Carvajal syndrome, a kind of cardiocutaneous syndrome.<sup>23</sup> Plakoglobin mutation leads to Naxos disease, another cardiocutaneous syndrome.



**Figure 1** The structural schematic diagram of desmosome. IDP, inner dense plaque; ODP, outer dense plaque; PM, plasma membrane; DSG2, desmoglein-2; DSC2, desmocollin-2; JUP, plakoglobin; PKP2, plakophilin-2; DSP, desmoplakin; IF, intermediate filaments.

cell death, acute mononuclear cell infiltration, and right ventricular aneurysm formation. However, interrogation for occurrence of enteroviral genome in association with ARVC has yielded contradicting results.<sup>34–36</sup>

According to Thiene et al.,<sup>37</sup> the histopathological alterations associated with ARVC development may follow three stages, namely: (i) acute, characterized by sarcolysis and inflammatory infiltration; (ii) subacute, with active fibrosis and dying myocytes, lymphocytes, and macrophages, or otherwise adipocytes replacing vanished myocytes; and (iii) chronic, in which fibrous tissue and adipocytes surround residual surviving myocytes.

## Apoptotic theory

Apoptosis, a form of programmed cell death, is essential to both foetal development and postnatal remodelling of the human heart.<sup>38</sup> However, abnormal perpetuation of apoptotic signals or the absence of antiapoptotic mechanisms may lead to abnormal progressive loss of RV myocytes. Unlike epithelial cells, myocytes are permanent and unable to counterbalance apoptosis through mitosis; in ARVC, the empty spaces left by dead myocytes are filled by adipocytes, fibrocytes, or both. In independent studies, the defender against apoptotic cell death (DAD1) gene and a gene associated with some familial cases of ARVC have been mapped to chromosome 14; however, it remains to be determined if they overlap.<sup>39,40</sup>

Using terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labelling (TUNEL) in autopsy specimens from ARVC patients, Mallat et al.<sup>41</sup> documented high levels of CCP-32 expression (a necessary specific protease for apoptotic cell death in mammalian cells<sup>42</sup>) along with morphological features of apoptosis, which is consistent with the study by Yamaji et al.<sup>43</sup> Because the TUNEL method cannot distinguish non-specific DNA degradation,<sup>44</sup> the possibility remained that post-mortem autolytic cell death could have accounted for the latter findings; however, apoptosis was also documented in a study of endomyocardial biopsies from 20 living patients using electron microscopy and the TUNEL method.<sup>45</sup> In the latter study, the presence of apoptosis significantly correlated with clinical duration of <6 months ( $P < 0.01$ ) and the presence of acute symptoms and signs ( $P = 0.007$ ), without significant difference in apoptotic index between children and adults ( $1.4 \pm 0.4$  vs.  $1.6 \pm 0.5\%$ , respectively).<sup>46</sup>

Despite efforts to underscore the role of apoptosis in ARVC pathogenesis, not all patients examined showed evidence of apoptosis and its triggers remain to be elucidated. To this end, *in vitro* and *in vivo* evidences from animal studies indicate that hypoxia as well as reperfusion injury might trigger apoptosis in cardiomyocytes, and it has been hypothesized that repeated ventricular arrhythmias in ARVC might produce ischaemia-reperfusion injury and further induce apoptosis.<sup>41</sup>

## Gene mutation theory

### Plakoglobin and desmoplakin gene mutations

Two mutations of the *JUP* gene encoding the cell adhesion protein JUP have disparate effects in ARVC: one leads to truncation of the

protein's C-terminus causing Naxos disease, a recessive cardiocutaneous syndrome characterized by woolly hair, palmoplantar keratoderma and the typical cardiac features of ARVC,<sup>17</sup> while the other results in insertion of an extra serine residue in the protein's N-terminal region causing autosomal dominant inheritance of ARVC but without apparent hair or skin abnormalities.<sup>47</sup>

A mutation in the *DSP* gene encoding another cell adhesion protein, DSP, truncates its C-terminal domain and also can underlie Naxos disease, while a mutation that truncates the intermediate filament-binding site of DSP results in a variant of Naxos disease with predominantly LV involvement, early morbidity, and clinical overlap with dilated cardiomyopathy (Carvajal syndrome).<sup>48</sup>

JUP may contribute to ARVC pathogenesis through: (i) suppression of the canonical Wnt/ $\beta$ -catenin signalling pathway (Figure 2), (ii) calcium homeostasis interference, and (iii) apoptosis.

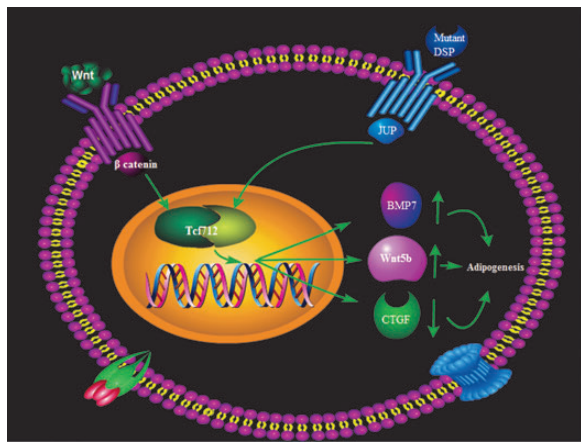
Mutant proteins could alter binding interactions within the desmosome, and the affected desmosomal proteins may translocate from junctional to cytosol compartments, potentially changing nuclear signalling and gene expression.<sup>49</sup>

JUP (also named  $\gamma$ -catenin) functions similarly to  $\beta$ -catenin, localizing both to the plasma membrane and the nucleus.<sup>50</sup> In cultured atrial myocytes (HL-1) without DSP and in an established cardiac-restricted *DSP*-deficient mouse model, disruption of DSP frees JUP from the plasma membrane allowing it to translocate to the nucleus.<sup>51</sup> Nucleus location of JUP might underlie suppression of Wnt signalling. JUP competes against  $\beta$ -catenin for binding with Tcf712 (transcriptional factor 712), leading to a series of consequences, including increased expression of bone morphogenic protein 7 (BMP7) and non-canonical Wnt5b, and reduction of connective tissue growth factor (CTGF). BMP7 and Wnt5b are well known promoters of adipogenesis in contrast to CTGF, which is an inhibitor of adipogenesis, and the alterations described in their expression can ultimately lead to the pathological phenotype of ARVC.

Intercellular coupling at gap junctions depends on intercellular adhesion.<sup>52</sup> An alteration or deficiency in elements of the cardiac desmosome therefore might lead to gap-junction remodelling and arrhythmia induction.<sup>53</sup> Wnt-1 leads to accumulation of Connexin43 (Cx43) protein and formation of functional gap-junction channels in cardiac myocytes.<sup>54</sup> The loss of Wnt signalling by affecting Cx43 protein expression and gap-junction coupling therefore might underlie arrhythmogenesis in early ARVC. Moreover, gap-junction remodelling diffusely occurs in both normal (LV and interventricular septum) and pathological regions.<sup>49</sup>

Compared with the canonical Wnt/ $\beta$ -catenin signalling pathway theory, the calcium homeostasis interference theory for JUP's action requires further substantiation. In-frame insertional mutation in a yeast-two-hybrid screen revealed a novel interaction between mutant *JUP* and histidine-rich calcium-binding protein.<sup>47</sup> Although thus far unconfirmed in patient-derived tissues, this finding indicates that JUP may promote arrhythmias through disturbed calcium homeostasis mediated by the histidine-rich calcium-binding protein.

JUP also might be involved in apoptosis. In cell-line studies, JUP regulated expression of the antiapoptotic gene *BCL2* (which encodes B-cell CLL/lymphoma 2), and the Wnt/ $\beta$ -catenin signalling pathway modulated the apoptotic response in preadipocytes.<sup>55,56</sup>



**Figure 2** The suppression of Wnt/ $\beta$ -catenin signal pathway. Mutant DSP frees JUP from the plasma membrane, allowing it to translocate to the nucleus. Nucleus location of JUP might be the initiator of the suppression of Wnt signalling. Plakoglobin competes against  $\beta$ -catenin for binding with Tcf712 (transcriptional factor 712), further leading to a series of consequences, increased expression of BMP7 and non-canonical Wnt5b and reduction of CTGF. Bone morphogenic protein 7 and Wnt5b are well known promoters of adipogenesis as opposed to CTGF, which is inhibitor of adipogenesis. Ultimately, the pathological morphology of ARVC developed.

### Plakophilin-2 gene mutation

Despite the aforementioned advances in understanding on the genesis of ARVC-associated morphological changes, it remains unclear how mutations in mechanical junctions affect the heart rhythm. In terms of the impact of mechanical coupling on electrical coupling in ARVC, Oxford *et al.*<sup>57</sup> demonstrated in cultures of neonatal rat ventricular myocytes that the ARVC-associated R79x truncation mutation of *PKP2* resulted in inhibition of *PKP2* expression; reduced expression and abnormal subcellular localization of Cx43; and reduced DSP expression.<sup>58</sup> In contrast, the 179fs frameshift mutant of *PKP2* did not affect either Cx43 or DSP expression.

Reduced sodium channel availability is considered much more likely to lead to abnormal propagation in ventricular muscle than in gap junctions.<sup>59</sup> The novel concept of 'the intercalated disc interactome' therefore was proposed,<sup>60</sup> to reflect that previously thought independent structures in the intercalated disc, including the desmosome, gap junction, and sodium channel, interact with each other and further result in arrhythmias in ARVC. *PKP2*, Cx43, and ankyrin-G (AnkG) have been studied as representative proteins of the desmosome, gap junction, and sodium channel, respectively. The loss of *PKP2* expression not only induced total Cx43 decrease and its distribution to the intracellular space, but altered the properties of the sodium current and the velocity of action potential propagation, which might provide a key substrate for arrhythmias and even sudden cardiac death during the 'concealed' phase of ARVC. In addition to a decrease in intercellular adhesion strength and electric coupling, the lack of AnkG expression led to changes in subcellular distribution and/or abundance of *PKP2* and Cx43. Moreover, as a

gap-junction protein, Cx43 plays a role in maintaining sodium current amplitude in cardiac myocytes. Arrhythmogenic right ventricular cardiomyopathy therefore would appear to be a disease of the intercalated disc rather than one of the desmosome.

### Desmoglein-2 gene mutation

As the only DSG isoform expressed in cardiomyocytes, mutations of *DSG2* have been reported recently in eight probands, with typical phenotype of ARVC characterized by predominantly right ventricular involvement and fibrofatty replacement of affected myocardium.<sup>15</sup>

### Desmocollin-2 gene mutation

Gerull *et al.*<sup>61</sup> have recently identified a homozygous truncation mutation, c. 1660C > T (p.Q554X) in *DSC2*, in affected individuals and determined a carrier frequency of this mutation of 9.4% (1 in 10.6) among 1535 Schmiedeleut Hutterites, suggesting a common founder in that subgroup. In the report, several individuals were observed with severe forms of biventricular cardiomyopathy characterized by mainly left-sided localized aneurysms, regions of wall thinning with segmental akinesis, in addition to typical electric and histological features known for ARVC.

### Peroxisome proliferator-activated receptor theory

The peroxisome proliferator-activated receptor (PPAR) family of ligand-activated transcription factors plays a critical role in regulating cellular lipid metabolism. Peroxisome proliferator-activated receptor alpha regulates cardiac fatty acid utilization pathways in various mouse models.<sup>62–64</sup> Despite its particularly high expression in white adipose tissue, PPAR $\gamma$  has been detected in the coronary arteries, aorta, left ventricle, and atrium of human heart.<sup>65,66</sup> The hypothesis was tested that changes in PPAR signalling contributed to myocardium fatty acid accumulation and contractile dysfunction in ARVC.<sup>67</sup> Interestingly, opposite changes between PPAR $\alpha$ - and PPAR $\gamma$ -dependent pathways were reported. Protein levels and mRNA of PPAR $\alpha$  were down-regulated in the RV and LV suggesting a global impairment of fatty acid  $\beta$ -oxidation in both ventricles, whereas a dramatic increase in PPAR $\gamma$  was observed only in the RV. In ARVC hearts, the decreases in PPAR $\alpha$  and  $\beta$ -oxidation might favour accumulation of fatty acids, which could then act as activators of PPAR $\gamma$ ; the resulting induction of PPAR $\gamma$  target genes could, in turn, amplify the imbalance between fatty acid supply and their  $\beta$ -oxidation, creating conditions for overt lipid accumulation, which would ultimately lead to the fat infiltration morphology in ARVC.

### Transforming growth factor beta-3 gene mutation

Two transforming growth factor beta-3 (*TGF $\beta$ -3*) mutant loci with single-nucleotide substitutions, namely (c. -36G > A) in the 5' untranslated region and (c. 1723C > T) in the 3' untranslated region, first evinced the association between *TGF $\beta$ -3* mutations and inherited human cardiac diseases.<sup>10</sup> Mutations in *TGF $\beta$ -3* might promote desmosomal dysfunction and cardiac remodelling, which would



provide a basis for the development of life-threatening arrhythmias; myocardial fibrosis might also be induced by the mutations.

## Cardiac ryanadine receptor 2 gene mutation

Delayed after-depolarization attributable to abnormal activation of sarcoplasmic reticulum  $\text{Ca}^{2+}$  release is the primary cause of cardiac ryanadine receptor 2 (RyR2)-associated cardiac arrhythmias.<sup>68</sup> Cardiac ryanadine receptor 2 N-terminal mutations recently were found to reduce the threshold for  $\text{Ca}^{2+}$  release termination and increased fractional release, which might underlie cardiomyopathy development in ARVC.<sup>69</sup>

## Transmembrane protein 43 gene mutation

In transfected COS-7 cells, Rajkumar et al.<sup>70</sup> found no evidence that mutant transmembrane protein 43 disrupts structure and function of desmosomal proteins leading to ARVC.

## Desmin gene mutation

Desmin (DES), which is the main intermediate filament of myocytes and also might be associated with ARVC, forms a flexible web-like cytoplasmic framework. Desmin mutations have severe consequences including formation of inclusion bodies, weakening of the DES cytoskeleton, disruption of subcellular organelle organization, and eventually myofibril degradation. Although mutations in the C-terminus of DES were associated with cardiomyopathies and/or cardiac arrhythmias,<sup>71</sup> desminopathies were often connected with skeletal muscles. In two Dutch families, ARVC-like or biventricular cardiomyopathy phenotypes were linked to mutations in the tail domain of DES, firstly bridging DES mutations and ARVC.<sup>72</sup> The genetic screen for the probands (presenting with early cardiac arrhythmias and later muscle weakness) and their families revealed two transition mutations within the coding region of DES resulting in N342D and R454W amino acid substitutions, and underscoring the relationship between DES mutations and ARVC development.

## Conclusion

Inflammation appears to interact with apoptosis in the etiopathogenesis of ARVC.<sup>37</sup> Abnormal and recurrent bouts of apoptosis might increase susceptibility to infection while, consistent with the finding of apoptosis during the 'acute phase' of histopathological alterations, myocardial inflammation with leucocyte infiltration might trigger apoptosis. Genetic defects of cellular receptors and/or altered immunological status also might increase viral susceptibility, leading to myocarditis, myocyte death, and finally fibrofatty replacement.<sup>32</sup> Notably, exertion also plays a critical role in the provocation and development of ARVC. In JUP<sup>+/-</sup> murine model, endurance training was observed to accelerate the development of right ventricular dysfunction and arrhythmias.<sup>73</sup>

The apparent interconnectivity among proposed theories for ARVC pathogenesis is consistent with ARVC probably being the result of the concomitant action of non-mutually exclusive pathogenetic mechanisms. Beyond those discussed in this review, four novel gene mutations, namely CTNNA3, LMNA, PLN, and TNN, have

successively been associated with ARVC,<sup>19–22</sup> and more are likely to emerge. Every gene mutation appears to lead to ARVC through its own mechanism; however, the underlying connections reviewed here suggest that the various gene mutations may ultimately result in ARVC through a 'final common pathway' whose elucidation warrants extensive research.

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# Balloon anchoring to exchange a displaced left ventricular lead over a wire without a coronary sinus guide catheter

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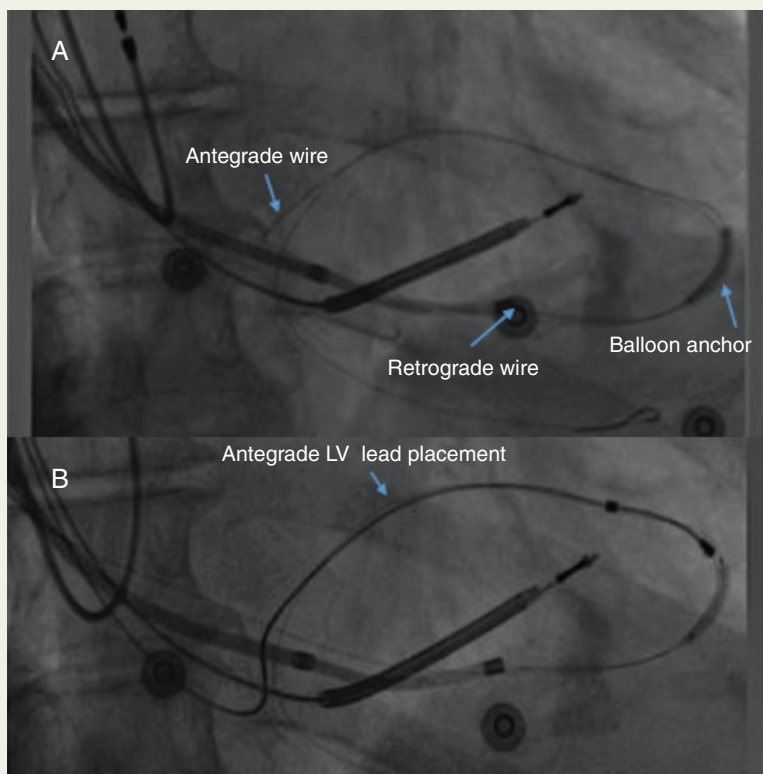
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A 59-year-old woman with a non-ischaemic cardiomyopathy was brought forward for a cardiac resynchronization therapy defibrillator device. Coronary sinus venography revealed a single posterior-lateral target branch and left ventricular (LV) lead placement proved challenging with the only trackable lead (4 F unipolar) placed following wire externalization. Unfortunately, this displaced within 24 h and a repeat procedure was required.

The LV lead had displaced proximally but the tip remained in the target branch which was wired antegradely through the lead and advanced into the middle cardiac vein (MCV) via collateral vessels and back into the right atrium.

The MCV was cannulated and venography demonstrated the patency of the collateral vessels to the target vein. A guidewire was introduced retrogradely from the MCV to the target branch and into the RA. Over this guidewire, a 2.5 × 15 mm compliant balloon was passed retrogradely and deployed in the postero-lateral branch to anchor the antegrade wire in position and provide support. The LV lead was then removed (Panel A).

The antegrade guidewire was then used to pass a new LV electrode (Panel B). Only the wire and the balloon anchor provided support. The lead advanced to a final position and the anchor balloon withdrawn.



The full-length version of this report can be viewed at: <http://www.escardio.org/Guidelines-&Education/E-learning/Clinical-cases/Electrophysiology/EP-Case-Reports>.