Molecular and Cellular Basis of Cardiomyopathies

Praveena Krishnakumar, Kabir Matwala, Shiv-Raj Sharma, and Salomon Narodden

What You Will Learn in This Chapter

This chapter will begin by defining the term 'cardiomyopathy'. From there, a comprehensive overview of the five main cardiomyopathies will be provided, both discussing the clinical signs and symptoms it manifests as, and also the science that underlies these changes. Where relevant, specific genetic mutations will be explored. This chapter ties together themes from earlier in the book, including the arrhythmogenicity of macro-reentrant circuits, the concept of contractility and the cardiomyocyte microstructure. Finally, new research surrounding Takotsubo cardiomyopathy will be explored.

Learning Objectives

- Discuss the causes of hypertrophic cardiomyopathy and the phenotype this produces.
- Understand the distinct phenotypes of the five primary cardiomyopathies.
- Appreciate the role of desmosome protein mutations in the development of arrhythmogenic right ventricular cardiomyopathy (ARVC).

12

12.1 Cardiomyopathy: The Fundamentals

'*Cardiomyopathy*' refers to a collection of 'myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular and congenital heart disease sufficient to cause the observed myocardial abnormality' [1]. First coined in 1952, this term came to refer three separate variants over the following decade, namely, *hypertrophic* (HCM), *dilated* (DCM) and *restrictive* (RCM) cardiomyopathies [2]. Subsequent imaging advances in the following resulted in the inclusion of further entities including *arrhythmogenic right ventricular* (ARVC) and so-called '*unclassified*' cardiomyopathies such as *Takotsubo*, also referred to as 'stress cardiomyopathy' and 'acute broken heart syndrome'. Importantly, with a prerequisite of this definition being both structural and functional abnormality, it therefore excludes channelopathies such as long QT and Brugada syndromes.

Of the five major categories of so-called 'primary cardiomyopathy' discussed, each can be classified into one of three major groups shown in ◘ Fig. 12.1, namely, genetic, acquired and mixed.

◘ **Fig. 12.1** Classification of the five main variants of primary cardiomyopathy
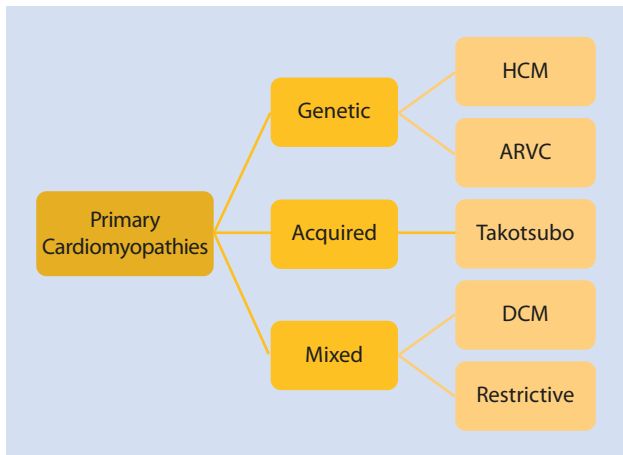
Catalysing the development of such categories has been an intensive effort to characterise genetic factors underlying the familial link of both the genetic and mixed cardiomyopathy phenotypes.

12.2 Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM), first described by Donald Teare in 1958, is characterised by cardiac hypertrophy independent of loading conditions, a non-dilated left ventricle (LV) and a normal or increased ejection fraction (EF) [3, 4]. It is mostly an autosomal disorder with variable penetrance [5]. HCM affects the sarcomere proteins and its associated protein, very rarely caused by autosomal recessive and X-linked modes of inheritance (e.g. Noonan syndrome [6], and Anderson–Fabry disease [7]. The commonest (30–50%) mutation is a missense (substitution) affecting gene *Myh7*, resulting in pathological alteration of ATPase activity and force generation of β-myosin heavy chains [8].

The second most common (20–40%) mutation affects gene *Mybpc3* and is a frameshift mutation caused by insertion/deletion that has phenotypic consequences on myosin-binding protein C [9]. A smaller proportion of patients (5–20%) exhibit mutations to *Tnnt2*, a gene encoding an essential component of the cardiac troponin T complex required for actomyosin interactions in response to Ca^{2+} [10]. Other less frequently affected genes are *Tpm1* (α-tropomyosin) and *Tnni3* (cardiac troponin I), both of which have an incidence of <5%.

As previously discussed, the classical HCM phenotype is asymmetrical hypertrophy of the LV, typically affecting the basal interventricular septum with LV outflow tract (LVOT) obstruction. Of course, other phenotypic variants of HCM also exist, namely, mid-cavity, concentric, apical and biventricular hypertrophy, in addition to concentric hypertrophic with cavity obliteration, and also progressive LV wall thinning [11–14].

Symptomatically, typical HCM manifestations include fatigue, dyspnea, presyncope or syncope, chest pain and palpitations, although patients may rarely be asymptomatic [7]. The presence of LVOT obstruction may be asymptomatic until the commencement of exercise. The majority of HCM patients also exhibit non-specific ECG abnormalities of hypertrophy, with a variable proportion having repolarisation abnormalities, abnormal Q-waves and inverted T-wave [8].

The echocardiographic hallmarks of HCM are the appearance of hypertrophy as described above, with potential haemodynamic features of LVOT obstruction and systolic anterior motion of the mitral valve [7]. Valsalva, exercise or pharmacological stressors such as dobutamine or nitrate-based agents could accentuate or unmask LVOT obstruction [15]. Histopathological features of HCM may include myocyte hypertrophy, an irregular 'chaotic' distribution of cells and unorthodox-shaped nuclei, and the presence of interstitial and replacement fibrosis. The intramural coronary arteries often appear with thickened vessel walls and a decreased lumen size [16]. A combination of these factors precipitates potential complications of heart failure (HF), sudden cardiac death (SCD) and stroke from an increased risk of atrial fibrillation [7].

12.3 Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) is defined by the dual presence of LV dilatation and contractile dysfunction. It is a mixed cardiomyopathy, with acquired DCM constituting the

majority of cases and deriving from a variety of aetiological factors. Up to 40% of cases are due to genetic factors, with over 40 causative genetic mutations identified [17]. These affect proteins of the sarcomere [18] (most frequently truncation mutations affecting titin [19], *Ttn*, but also myosin, *Myh6*, *Myh7*, *Mybpc3*; and actin, *Actc1* and *Actc2*), cytoskeleton [20] (desmin and cypher/ZASP), nuclear envelope [21] (limb-girdle muscular dystrophy, Emery–Dreifuss muscular dystrophy and autosomal dominant partial lipodystrophy), sarcolemma, ion channels and intercellular junctions. The latter two do not strictly belong to 'primary muscle disorders' to fit the definition of DCM.

In adult DCM, the usual mode of transmission is mostly autosomal dominant, commonly with partial and age-related penetrance and variable expression [22]. In paediatric and adolescent forms, autosomal recessive is the most common transmission pattern [23]. Phenotypically, DCM manifests as LV dilatation with impaired function (LVEF <40%) in the absence of hypertension, valvular heart disease and coronary heart disease [24]. The echocardiographic features of DCM include spherical dilatation of the LV, mitral regurgitation from annular dilatation and the potential appearance of pulmonary hypertension [24]. The global systolic cardiac function is reduced, and the diastolic function may show a restrictive filling pattern.

Patients with DCM may be asymptomatic for a number of years, with SCD an uncommon but notable first presentation of the disease. Typically, symptoms of HF occur over time, namely, a reduced exercise tolerance, dyspnoea and palpitations [25]. In contrast, the non-genetic (acquired) causes of DCM are diverse, some of which shown below in ◘ Table 12.1 [26–29].

12.4 Restrictive Cardiomyopathy (RCM)

12

Restrictive cardiomyopathy (RCM) is the least common of the three subtypes in the original 1952 definition and appears phenotypically as a non-dilated left or right ventricle with normal wall thickness [30]. Diastolic dysfunction may reveal as restrictive filling (due to

◘ **Table 12.1** A summary of some notable non-genetic causes of DCM

Acquired causes of DCM	Examples
Infection	Adenovirus, coxsackie, HIV, cytomegalovirus, rheumatic fever, typhoid fever, syphilis, leptospirosis, histoplasmosis, toxoplasmosis
Prescribed drugs	Cyclophosphamide, zidovudine, clozapine
Toxins	Cocaine, alcohol, amphetamine, lead
Electrolyte imbalances	Uraemia and hypocalcaemia
Autoimmune pathology	SLE, scleroderma, dermatomyositis, rheumatoid arthritis
Endocrine pathology	Hypo/hyperthyroidism, gross hormone excess or deficiency, phaeochromocytoma

Information adapted from [26–29]

◘ Table 12.2 A summary of some notable causes of RCM	
Familial causes of RCM	**Examples**
Endomyocardial	Sarcomeric protein mutations, troponin I (RCM +/− HCM), pseudoxanthoma elasticum, desminopathy
Infiltration	Essential myosin light chains and familial amyloidosis
Storage	Haemochromatosis, Anderson–Fabry disease, glycogen storage disease (type II, III, IV)
Non-familial causes of RCM	
Endomyocardial	Scleroderma, radiation, fibrosis-inducing drugs (e.g. serotonin, methysergide, ergotamine)
Infiltration	Metastatic cancers
Information adapted from [30–32]	

decreased myocardial compliance) with elevated filling pressures and dilated atria. Systolic function is often preserved, albeit not completely normal [30]. Classical symptoms of RCM include dyspnoea, peripheral oedema, ascites, palpitations, fatigue, weakness and exercise intolerance. Diagnosis is usually made via exclusions. As a mixed cardiomyopathy, its cause in any given patient can be classified into familial (genetic) or non-familial (acquired), with the majority of cases being the latter [30]. Some of these are shown in ◘ Table 12.2 [30–32]. Mutations to genes encoding several sarcomeric proteins have been associated with RCM when inherited in an autosomal dominant manner, namely, β-myosin heavy chain (*Myh7*), actin (*Actc*), troponin I (*Tnni3*) and troponin T (*Tnnt2*) [33].

12.5   Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease characterised by the progressive replacement of myocardium by fibrofatty tissue in the RV [34]. Although non-ischaemic, the loss of myocardium results in regions of hypokinetic tissue, compromising the ventricle's contractile capability. Typically, this deposition of fibrofatty tissue is initially localised to three areas: the inflow tract, outflow tract and RV apex in an arrangement referred to as the 'triangle of dysplasia' [35]. Whilst predominating in the RV, advanced cases of ARVC frequently involve the left ventricle as well, in addition to some subvariants of ARVC concentrated in the LV [36]. ARVC manifests as symptoms including syncope and shortness of breath (dyspnoea), both of which derive from compromised RV contractility and thus output, in addition to palpitations.

Importantly, it is not uncommon for the first presentation of ARVC to be sudden cardiac death (SCD), particularly in young adults and competitive athletes [37]. In one study conducted over a 10-year period in Veneto, Italy, ARVC constituted the most frequently encountered cause of sudden cardiac death in young adults, accounting for 27% of 22 cases [37].

Potentially underlying the association between the symptomatic expression of ARVC (including SCD) and exercise is the increased myocardial workload and subsequent adrenergic signalling. This is superimposing on a tissue interspersed with fibrofatty tissue that will slow conduction, providing a suitable substrate for the generation of macro-reentrant circuits and ventricular arrhythmias [38].

ARVC is considered a genetic cardiomyopathy and is usually inherited in an autosomal dominant manner, with incomplete penetrance and a variable expression pattern. That said, some rare recessive cases have been noted [39]. Across several studies, causative mutations are typically identified in 30–50% of affected individuals, with a high proportion being in genes encoding desmosomal proteins [38]. It was only following this discovery that AVRC, originally considered a congenital defect of the right ventricle, was re-classified as a cardiomyopathy [38]. Desmosomes are a subset of junctional complex that confers stronger intercellular adhesion in order to maintain the global structural integrity of a tissue [40]. They are particularly abundant in tissues exposed to significant mechanical stress, such as the mucosa of the gastrointestinal tract, the epidermis and the myocardium, to name a few [40].

A desmosome comprises five structural elements, namely, plakoglobin, plakophilin-2, desmoplakin, desmoglein-2 and desmocollin-2. The encoding gene of each of the desmosome proteins is shown in ◘ Table 12.3.

In a seminal 2000 paper by McKoy et al., mutations in the gene encoding plakoglobin, *Jup*, were the first identified as contributing towards the development of ARVC [41]. This finding renewed interest on intercellular adhesion proteins, with subsequent causative mutations later identified in each of the genes encoding the other four proteins. The most frequently mutated of these is plakophilin-2, encoded by *Pkp2*, with one study of 120 unrelated ARVC individuals identifying heterozygous *Pkp2* mutations in 26.7% of cases [42].

The importance of desmosomes in the pathophysiology of ARVC is further supported by Basso et al. who used transmission electron microscope (TEM) to study the ultrastructure of intercalated discs obtained from ARVC patients. These were then compared against both control and DCM samples. The ARVC intercalated discs exhibited marked structural remodelling, including a reduction in the number of desmosomes and substantial elongation of those remaining. With desmosomes being the vital mechanical support structure of intercalated discs, a depletion in their representation represents a marked deterioration in the architectural stability of the heart as a functional syncytium. Specifically, with this reduction localised to the intercalated discs of the RV, a sudden increase in mechanical stress, such as that encountered during exercise, would represent a weakening of intercellular junctions in the ventricle.

12

◘ **Table 12.3** Table of the five constituent desmosome proteins and their encoding genes

Desmosome protein	Encoding gene
Plakoglobin	*Jup*
Plakophilin-2	*Pkp2*
Desmoplakin	*Dsp*
Desmoglein-2	*Dsg2*
Desmocollin-2	*Dsc2*

12.6 Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM) was first discovered in 1990 by Sato et al. and derives its name from the Japanese word '*takotsubo*', meaning 'octopus pot' [43]. This is due to the apical ballooning of the LV and resemblance this has to the aforementioned pot. Broadly, TCM has come to be characterised by transient and reversible systolic dysfunction concentrated in the middle and apical segments of the LV, with subsequent hypercontractility in the base of the heart [44].

Due to its association with physical and/or emotional stress, both of which frequently represent triggers of this cardiomyopathy, Takotsubo has also come to be known as 'stress cardiomyopathy' or 'acute broken heart syndrome' [43, 44]. Indeed, this is evidenced by Paur et al., who used an in vivo rat model to demonstrate the induction of mid-LV-to-apical hypocontractility (TCM) using high-dose IV adrenaline [44].

Likely underlying this distinctive phenotype is the heterogeneous distribution of β-adrenergic receptors (βAR) throughout the mammalian myocardium, with the apex characterised by the densest dispersion of receptors relative to the sparse proportion in the base [45, 46]. They form a broad βAR-response gradient that has been evidenced in several animal models [44, 47, 48].

Constituting ~90% of the total cardiac adrenergic receptors, βAR mediate many of the sympathetic nervous system (SNS) effects on the heart [49]. Briefly, catecholamines (especially adrenaline) bind to and activate βAR, triggering the exchange of GDP for GTP on the associated G_s alpha subunit. This facilitates dissociation of the G-protein, which is now able to activate adenylyl cyclase (AC), a 12-transmembrane domain enzyme that catalyses the conversion of ATP to cyclic 3′,5′-adenosine monophosphate (cAMP) and pyrophosphate using its C1a and C2a domains. Protein kinase A (PKA) is a holoenzyme composed of two regulatory and two catalytic subunits. cAMP binds to the two PKA regulatory subunits, causing dissociation from the catalytic subunits, which are now able to phosphorylate proteins, exerting many of the adrenergic effects, including positive inotropy (discussed further in ► Chap. 10).

However, $β_2AR$ is also able to exert signalling via an alternative G_i alpha subunit (and non-G-protein pathways altogether), with subsequent negative inotropic effects on the myocardium [44]. At high levels, adrenaline can 'switch' $β_2AR$ signalling to this pathway via the G_i alpha subunit in a process termed 'biased agonism'. Consequently, at high adrenaline concentrations, the differential apical–basal expression of $β_2AR$ produces intraventricular variability in inotropy and the Takotsubo phenotype [44]. For this reason, TCM is classified as an acquired cardiomyopathy.

> **Take-Home Message**
> - 'Cardiomyopathy' refers to myocardial disorders in which the heart is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular or congenital heart disease sufficient to cause the observed myocardial abnormality.
> - Primary cardiomyopathies can be classified into genetic (HCM, ARVC), acquired (TCM) and mixed (DCM, RCM) categories.
> - Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterised by the progressive replacement of myocardium by hypokinetic fibrofatty tissue, resulting in a loss of contractility in affected regions.

References

1. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P et al (2008) Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur Heart J 29(2):270–276

2. Yacoub MH (2014) Decade in review – cardiomyopathies: cardiomyopathy on the move. Nat Rev Cardiol 11:628

3. Teare D (1958) Asymmetrical hypertrophy of the heart in young adults. Br Heart J 20(1):1–8

4. Marian AJ, Braunwald E (2017) Hypertrophic cardiomyopathy. Circ Res 121(7):749–770

5. Maron BJ (2002) Hypertrophic cardiomyopathy. JAMA 287(10):1308–1320

6. Hickey EJ, Mehta R, Elmi M, Asoh K, McCrindle BW, Williams WG et al (2011) Survival implications: hypertrophic cardiomyopathy in Noonan syndrome. Congenit Heart Dis 6:41

7. Semsarian C, Ingles J (2013) Expanding the genetic spectrum of hypertrophic cardiomyopathy: X marks the spot. Circ Cardiovasc Genet 6:528

8. Bonne G, Carrier L, Richard P, Hainque B, Schwartz K (1998) Familial hypertrophic cardiomyopathy: from mutations to functional defects. Circ Res 83:580

9. Maron BJ, Maron MS, Semsarian C (2012) Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 60:705

10. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C et al (2003) Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation 107:2227

11. Kim EK, Lee SC, Hwang JW, Chang SA, Park SJ, On YK et al (2016) Differences in apical and non-apical types of hypertrophic cardiomyopathy: a prospective analysis of clinical, echocardiographic, and cardiac magnetic resonance findings and outcome from 350 patients. Eur Heart J Cardiovasc Imaging 17:678

12. Bejiqi R, Retkoceri R, Bejiqi H (2011) Hypertrophic cardiomyopathy associated with mid-cavity obstruction and high left intraventricular pressure. Acta Inform Medica 19(4):241

13. Yamaguchi H, Ishimura T, Nishiyama S, Nagasaki F, Nakanishi S, Takatsu F et al (1979) Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. Am J Cardiol 44(3):401–412

14. Olivotto I, Cecchi F, Poggesi C, Yacoub MH (2012) Patterns of disease progression in hypertrophic cardiomyopathy an individualized approach to clinical staging. Circ Hear Fail 5:535

15. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT et al (2006) Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 114:2232

16. Hughes SE (2004) The pathology of hypertrophic cardiomyopathy. Histopathology 44:412

17. Mestroni L, Brun F, Spezzacatene A, Sinagra G, Taylor MR (2014) Genetic causes of dilated cardiomyopathy. Prog Pediatr Cardiol 37(1–2):13–18

18. Kamisago M, Sharma SD, DePalma SR, Solomon S, Sharma P, McDonough B et al (2000) Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. N Engl J Med 343:1688

19. Herman DS, Lam L, Taylor MRG, Wang L, Teekakirikul P, Christodoulou D et al (2012) Truncations of titin causing dilated cardiomyopathy. N Engl J Med 366:619

20. Sequeira V, Nijenkamp LLAM, Regan JA, Van Der Velden J (2014) The physiological role of cardiac cytoskeleton and its alterations in heart failure. Biochim Biophys Acta Biomembr 1838:700

21. Dellefave L, McNally EM (2010) The genetics of dilated cardiomyopathy. Curr Opin Cardiol 25:198

22. Hershberger RE, Morales A (1993) Dilated cardiomyopathy overview [Internet]. GeneReviews®. University of Washington, Seattle. [cited 2019 Jan 29]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20301486

23. Mestroni L, Rocco C, Gregori D, Sinagra G, Di LA, Miocic S et al (1999) Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. Heart Muscle Disease Study Group. J Am Coll Cardiol 34:181

24. Thomas DE, Wheeler R, Yousef ZR, Masani ND (2009) The role of echocardiography in guiding management in dilated cardiomyopathy. Eur J Echocardiogr 10:iii15

25. Michels VV, Driscoll DJ, Miller FA, Olson TM, Atkinson EJ, Olswold CL et al (2003) Progression of familial and non-familial dilated cardiomyopathy: long term follow up. Heart 89:757

12

26. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL et al (2000) Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 342:1077

27. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M et al (2016) Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J 37:1850

28. San Martín MA, García A, Rodríguez FJ, Terol I (2002) Dilated cardiomyopathy and autoimmunity: an overview of current knowledge and perspectives. Rev Esp Cardiol 55(5):514–524

29. Schürer S, Klingel K, Sandri M, Majunke N, Besler C, Kandolf R et al (2017) Clinical characteristics, histopathological features, and clinical outcome of methamphetamine-associated cardiomyopathy. JACC Hear Fail 5:435

30. Muchtar E, Blauwet LA, Gertz MA (2017) Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res 121:819

31. Kaski JP, Syrris P, Burch M, Tomé Esteban MT, Fenton M, Christiansen M et al (2008) Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart 94:1478

32. Navarro-Lopez F, Llorian A, Ferrer-Roca O, Betriu A, Sanz G (1980) Restrictive cardiomyopathy in pseudoxanthoma elasticum. Chest 78:113

33. Towbin JA (2014) Inherited cardiomyopathies. Circ J 78(10):2347–2356

34. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N (1988) Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 318:129

35. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M (1996) Arrhythmogenic right ventricular cardiomyopathy: dysplasia, dystrophy, or myocarditis? Circulation 94:983

36. Norman M, Simpson M, Mogensen J, Shaw A, Hughes S, Syrris P et al (2005) Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation 112:636

37. Corrado D, Thiene G, Nava A, Rossi L, Pennelli N (1990) Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases. Am J Med 89:588

38. Lombardi R, Marian AJ (2010) Arrhythmogenic right ventricular cardiomyopathy is a disease of cardiac stem cells. Curr Opin Cardiol 25:222

39. Marcus FI, Edson S, Towbin JA (2013) Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol 61:1945

40. Garrod D, Chidgey M (2008) Desmosome structure, composition and function. Biochim Biophys Acta Biomembr 1778:572

41. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A et al (2000) Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 355:2119

42. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA et al (2004) Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 36:1162

43. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M et al (2015) Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med 373:929

44. Paur H, Wright PT, Sikkel MB, Tranter MH, Mansfield C, O'Gara P et al (2012) High levels of circulating epinephrine trigger apical cardiodepression in a β2-adrenergic receptor/Gi-dependent manner: a new model of takotsubo cardiomyopathy. Circulation 126:697

45. Mori H, Ishikawa S, Kojima S, Hayashi J, Watanabe Y, Hoffman JIE et al (1993) Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. Cardiovasc Res 27:192

46. Lyon AR, Rees PSC, Prasad S, Poole-Wilson PA, Harding SE (2008) Stress (Takotsubo) cardiomyopathy – a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med 5:22

47. Mantravadi R, Gabris B, Liu T, Choi BR, De Groat WC, Ng GA et al (2007) Autonomic nerve stimulation reverses ventricular repolarization sequence in rabbit hearts. Circ Res 100:e72

48. Lathers CM, Levin RM, Spivey WH (1986) Regional distribution of myocardial beta-adrenoceptors in the cat. Eur J Pharmacol 130(1–2):111–117

49. O'Connell TD, Jensen BC, Baker AJ, Simpson PC (2014) Cardiac alpha1-adrenergic receptors: novel aspects of expression, signaling mechanisms, physiologic function, and clinical importance. Pharmacol Rev 66(1):308–333