Pathophysiology

3

Valerio De Paris, Federico Biondi, Davide Stolfo, Marco Merlo, and Gianfranco Sinagra

Abbreviations and Acronyms

AD	Alzheimer's disease
ANP	Atrial natriuretic peptide
ARVC	Arrhythmogenic right ventricular Cardiomyopathy
AT1/2R	Angiotensin type 1/2 receptor
ATII	Angiotensin II
BNP	Brain natriuretic peptide
DCM	Dilated cardiomyopathy
ECM	Extracellular matrix
HF	Heart failure
IL1β	Interleukin 1 β
LV	Left ventricular
MCP-1	Monocyte chemoattractant protein-1
MIP 1α	Macrophagic inflammatory protein 1 α
MMP-9	Matrix metalloproteinase-9
PIIINP	N-terminal type III collagen peptide
RAAS	Renin-angiotensin-aldosterone system
RyR2	Ryanodine receptor 2
SERCA	Sarco-/endoplasmic reticulum Ca^{2+}-ATPase
SR	Sarcoplasmic reticulum
TIMP-1	Tissue inhibitor of metalloproteinase-1
TNFα	Tumor necrosis factor

V. De Paris · F. Biondi · D. Stolfo (✉)
Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, University of Trieste (ASUITS), Trieste, Italy
e-mail: Davide.stolfo@asuits.sanita.fvg.it

M. Merlo · G. Sinagra
Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, Trieste, Italy
e-mail: gianfranco.sinagra@asuits.sanita.fvg.it

G. Sinagra et al. (eds.), *Dilated Cardiomyopathy*,
https://doi.org/10.1007/978-3-030-13864-6_3

Dilated cardiomyopathy (DCM) is characterized by dilated left ventricle with systolic dysfunction that is not caused by ischemic or valvular heart disease.

The hallmark pathophysiologic feature of DCM is systolic dysfunction of the left or both ventricles. Reduced sarcomere contractility increases ventricular volumes to maintain cardiac output through the Frank-Starling mechanism, producing the thin-walled dilated LV appearance that is observed in overt DCM.

Frank and Starling demonstrated that increased ventricular preload augments contractility, but excessive pressure and volume induces a plateau and then a reduction in myocardial contraction [1]. Abnormal hemodynamics leads further to left ventricular (LV) remodeling.

Cardiac remodeling in response to an inciting myocardial insult or an underlying genetic abnormality has been classically considered the pathognomonic aspect of DCM.

3.1 Ventricular Remodeling in DCM

The term ventricular remodeling refers to alteration in ventricular architecture, with associated increased volume and altered chamber configuration, driven on a histologic level by a combination of pathologic myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis.

Pathologic LV remodeling is closely linked to activation of a series of neuroendocrine, paracrine, and autocrine factors, which are upregulated after myocardial injury and in the setting of increased LV wall stress and hemodynamic derangement. Contributing factors include the renin-angiotensin-aldosterone (RAA) axis, the adrenergic nervous system, increased oxidative stress, pro-inflammatory cytokines, and endothelin. Both RAA system inhibition and beta-adrenergic blockade have shown to markedly attenuate or reverse LV remodeling in patients with heart failure and LV dilation.

Left ventricular remodeling results in characteristic alterations of left ventricular function that can be described in terms of altered left ventricular pressure-volume relationship. Left ventricular dilatation and reduced systolic function induce a rightward displacement of the pressure-volume curve with increased left ventricular end-diastolic volumes and pressures. Despite increased preload, stroke volume may be reduced, and end-systolic pressure to volume ratio (index of contractility) is depressed. In addition to this, diastolic dysfunction due to incomplete relaxation after disturbed excitation-contraction coupling processes and increased stiffness due to altered extracellular matrix composition cause an additional upward shift of the pressure-volume relation.

When the preload reserve is exhausted, the stroke volume becomes sensitive to alterations in the afterload. It depends on blood viscosity, vascular resistance, vascular distensibility, and mainly myocardial wall tension.

Calculations of myocardial wall tension are defined by the Laplace equation and are expressed in terms of tension, T, per unit of cross-sectional area (dynes per centimeter [dyn/cm]).

Within a cylinder, the law of Laplace states that wall tension is equal to the pressure within a thick-walled cylinder times the radius of curvature of the wall:

$$T = P \times R / h$$

where T is wall tension (dyn/cm), P is pressure (dyn/cm^2), R is the radius (cm), and h is wall thickness.

Two fundamental principles stem from the relationship between the geometry of the ventricular cavity and the tension on its muscular walls: (1) dilatation of the ventricles leads directly to an increase in tension and (2) an increase in wall thickness reduces the tension on any individual muscle fiber. Therefore, ventricular hypertrophy reduces afterload by distributing tension among more muscle fibers.

Dilatation of the heart decreases cardiac efficiency as measured by myocardial oxygen consumption unless hypertrophy is sufficient to normalize wall stress. In HF, wall tension (or stress) is high, and thus, afterload is increased. The energetic consequences of the law of Laplace can have some role in progressive deterioration of energy-starved cardiac myocytes in the failing heart.

3.2 Genetic Pathophysiology and New Possible Proteins Involved in DCM [2]

A great diversity of pathogenetic pathways has been hypothesized to explain the development of DCM, depending on the affected genes and the dislodged intracellular structures or pathways.

The wide variety of genes involved in the pathophysiology of DCM gives an insight to think of DCM as a group of diseases, instead of a single form of cardiomyopathy (Fig. 3.1).

Genetic mutations suggest several mechanisms of ventricular dysfunction in DCM as follows:

- *Deficit in force generation* (*sarcomere DCM*): Mutations within genes encoding titin, myosin, actin, troponin, and tropomyosin result in the expression of abnormally functioning proteins, thus leading to myocardial dysfunction and DCM. Sarcomere gene mutations are the most frequent causes of DCM with truncating mutations in titin (TTNtvs) occur in 25% of end-stage disease and in 15% of ambulatory DCM patients [3, 4].
- *Defects in nuclear envelope* (*laminopathies*): These diseases are characterized by variable degrees of heart and skeletal muscle involvement. Mutations involve Lamin-A/C and emerin coding genes. Dominant Lamin A/C mutations occur in approximately 6% of DCM cases and are far more common in DCM with conduction system disease [5]. Electrophysiological abnormalities (conduction system block and atrial fibrillation) often precede DCM that relentlessly progresses to HF [6, 7]. The severity of the associated skeletal myopathy is variable. Most Lamin A/C mutations cause haploinsufficiency, and mouse models of these mutations demonstrate inadequate response to mechanical strain, which may promote premature cardiomyocyte death.

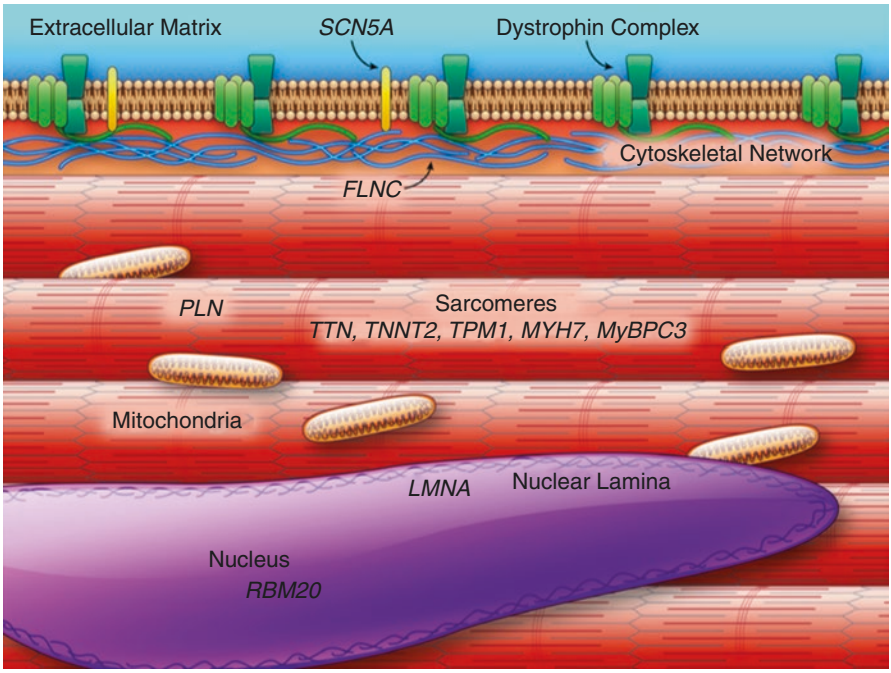

Fig. 3.1 Cardiomyocyte compartments contributing to genetically mediated dilated cardiomyopathy. See Legend for abbreviations and acronyms. (Adapted from McNally EM, Mestroni L, Dilated Cardiomyopathy Genetic Determinants and Mechanisms *CircRes*. 2017;121:731–748. DOI: https://doi.org/10.1161/CIRCRESAHA.116.309396)

- *Deficit in force transmission* (*cytoskeletal cardiomyopathies*): Mutations involving protein members of the cytoskeletal apparatus, like filamins, dystrophin, desmin, d-sarcoglycan, and vinculin, are responsible for muscular dystrophies, which are often associated with DCM.
- Filamins are large cytoskeletal actin cross-linking proteins that stabilize the actin filament networks and link them to the cell membrane by binding transmembrane proteins and ion channels [8]. Filamin C encodes a large protein (2725 amino acids) primarily expressed in the cardiac and skeletal muscle that interacts with sarcomeric proteins in the Z-disc and the sarcolemma. Filamin C truncation variants are associated with a severe arrhythmogenic DCM phenotype in the absence of overt skeletal muscle disease.
- *Deficit in protein post-translational modifications* (*glycosylation processes-cardiomyopathies*): An example comes from dolichol kinase gene mutations, resulting in impairment of protein glycosylation processes inside the cell organelles, thus manifesting as syndromic conditions with hypertrophic phenotype and as non-syndromic DCM phenotype [9].
- *Impaired cell-to-cell adhesion* (*desmosomal cardiomyopathies*): Mutations in genes encoding desmosomal proteins are responsible for arrhythmogenic right

ventricular Cardiomyopahty (ARVC) and also for DCM, with a prevalence of up to 13% in a DCM cohort [10].

- *Deficit in energy production* (*mitochondrial cardiomyopathies*): They are characterized by defects in the oxidative phosphorylation that result in deficient energy production in the form of ATP. They include hypertrophic, dilated, and LV non-compaction phenotypes.
- *Calcium-cycling abnormalities*: A DCM mutation has been described in the phospholamban gene. Phospholamban is responsible for inhibition of sarco-/endoplasmic reticulum $Ca2^{+}$ –ATPase (SERCA) function. Mutations in the gene result in increased SERCA inhibition with defective calcium reuptake, with consequent reduction in contractility and heart dilation.
- *Ion channel abnormalities*: Mutations in ion channel genes (SCN5A, ABCC9) are typically associated with a variety of arrhythmic disorders. The ventricular dilation and DCM pattern is less common and almost always preceded by arrhythmias and/or conduction system defects [11, 12]. The pathogenetic mechanisms are poorly understood.
- *Spliceosomal defects*: RBM20 is an RNA binding protein involved in alternative splicing process. DCM associated with RBM20 mutations is frequently associated with early onset, severe heart failure, and high arrhythmic potential.
- *Epigenetic perturbation*: Missense mutation in GATAD1 gene is associated with DCM. GATAD1 encodes for a protein that is thought to bind to a histone modification site that regulates gene expression.
- *Protein misfolding disease*: Mutations in presenilin genes have been recently identified in patients with DCM [13]. Presenilins are also expressed in the heart and play a role in heart development. Aβ amyloid is a possible novel cause of myocardial dysfunction. Echocardiographic measurements of myocardial function suggest that patients with Alzheimer's disease (AD) present with an anticipated diastolic dysfunction. As in the brain, A β40 and A β42 are present in the heart, and their expression is increased in AD [14].
- *RAS-MAPK pathway disruption*: Mutations in RAF-1 gene are responsible for rare variants of childhood-onset, non-syndromic DCM.

3.3 Molecular Mechanisms of Cardiac Remodeling in HF [15]

DCM is histologically characterized by diffuse fibrosis, compensatory hypertrophy of the other myocytes, and myocyte dropout. Myocyte hypertrophy is promoted by catecholaminergic stimulation, stretch activation of integrins by myocyte and fibroblast, G protein-mediated intracellular signaling, and micro-RNA networks. A new gene expression toward a fetal pattern results in profound morphological rearrangements. The rate of myocyte apoptosis and consequently progressive cells lost is increased in DCM. This process is partly favored by the elevated expression of fetal genes.

Neurohormonal systems. Acutely reduced cardiac output or vascular underfilling leads to baroreceptor-mediated sympathetic nervous activity with elevation of heart rate, blood pressure, and vasoconstriction. Although these changes maintain an

adequate cardiac output, at the end they lead to vicious circle. Catecholamines promote arrhythmias, myocardial ischemia, myocyte hypertrophy, and apoptosis and cause different signal-transduction abnormalities (e.g., beta-1 receptor downregulation) [16].

HF results from increased sympathetic nervous activity, but the renin-angiotensin-aldosterone system (RAAS) is also pathologically activated.

Angiotensin II (ATII) is the most powerful mediator of the RAAS. Its activity is mediated by two major G protein receptor associated receptors: angiotensin type-1 and type-2 receptor (AT1R and AT2R). AT1R is expressed mainly in the vasculature, kidney, adrenal cortex, lungs, and brain, and its activation promotes vasoconstriction; AT2R is mainly expressed in the myocardium and promotes vasodilatation and antiproliferative, anti-oxidative, and anti-inflammation effects.

ATII contributes to the increased activity of the sympathetic nervous system by stimulating the adrenal glands and the juxtaglomerular apparatus of the kidney with resulting elevation of plasma renin levels.

Furthermore, ATII stimulates adrenal secretion of aldosterone which, together with vasopressin, reduces renal excretion of water and sodium [17], configuring an inappropriate ADH secretion syndrome.

Finally, ATII contributes to cardiac remodeling promoting myocyte hypertrophy and apoptosis and structural and biochemical alterations in the ECM [18, 19].

Natriuretic peptides. Natriuretic peptides are hormones produced by the heart. The most important ones are atrial natriuretic peptide (ANP), mainly produced in the atria, and B-type natriuretic peptide (BNP) which is mainly released by ventricular myocardium. They are released in response to myocardial stretch and act as counter-regulatory hormones promoting natriuresis, diuresis, and vasodilation. Their plasma concentrations raise in proportion to HF severity and are consolidated markers of poor prognosis in overt HF.

Inflammation. Inflammation may also play a role in pathophysiology of DCM. Many studies have shown an increase in different inflammatory mediators (e.g., tumor necrosis factor α (TNFα), interleukin (IL) 1beta). IL-2, IL-6, Fas ligand, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein α (MIP-1α) in HF have also been renamed as an inflammatory disease.

TNFα, for example, has a negative inotropic toxic effect on the myocardium that is connected to adverse ventricular remodeling in DCM.

Extracellular matrix. The extracellular matrix in the heart provides the scaffolding within which contractile cardiomyocytes are housed; it contains a basement membrane, collagen network, proteoglycans, and glycosaminoglycans. Of the different types of collagens, type I and III collagens are the predominant forms found in fibrils deposited in scar tissue after myocardial injury, more specifically demonstrated in myocardial infarction models. These collagens are initially synthesized by cardiac fibroblasts as procollagen precursors before both the N-terminal and the C-terminal are cleaved by proteinases, and then the resulting tropocollagen is assembled into mature fibrils. Markers of collagen turnover such as serum N-terminal type III collagen peptide (PIIINP) have been associated with increased mortality and hospitalization rates, and procollagen type I and PIIINP levels appeared to

decrease following aldosterone antagonist therapy in chronic HF patients [20]. In the 967 Framingham subjects without HF, PIIINP levels were not independently associated with LV mass, fractional shortening, end-diastolic dimensions, or left atrial size [21].

The extracellular matrix is a rather dynamic system that is constantly turned over. In the setting of cardiac or extracardiac injury, regulation of extracellular matrix likely plays an important role in ventricular remodeling and fibrosis. For example, bone morphogenetic protein 1, a C-proteinase, plays a crucial role in the processing of extracellular matrix proteins and collagen deposition and regulation of excessive collagen deposition in fibrosis after tissue injury [22]. Recent studies have found that gene expression of tissue inhibitor of metalloproteinases-1 (TIMP-1) and matrix metallopeptidase-9 (MMP-9) was significantly increased in the border zone of myocardial infarct models as well as ischemic HF models in rats and that treatment with antifibrotic therapy can prevent the upregulation of MMP-9, ultimately leading to suppression of collagen deposition [23, 24]. Interestingly, concentrations of TIMP-1 appeared to correlate with diastolic LV dysfunction [25]. In a multimarker analysis of HF patients, a panel that included TIMP-1 as well as NT-proBNP, hs-TnT, growth differentiation factor 15, and insulin-like growth factor-binding protein 4 had the best performance in predicting all-cause mortality at 3-year follow-up.

Calcium. Cytoplasmic Ca^{2+} has a key role in cardiac contraction triggering the interaction of the myosin-thick and actin-thin myofilament. During the depolarization of the myocyte, Ca^{2+} enters the myocyte through L-type Ca^{2+} channels known as transverse tubules, which are close to the sarcoplasmic reticulum (SR) and stimulates the release of much greater quantities of Ca^{2+} from the SR into the cytoplasm through the Ca^{2+} release channels, the ryanodine receptors (RyR2). After reaching a critical concentration, the cytoplasmic Ca^{2+} activates the contractile system of the myocyte. The sarco-/endoplasmic reticular adenosine triphosphate-driven [Ca^{2+}] (SERCA2a) pump returns cytoplasmic Ca^{2+} to the SR against a concentration gradient, and this ends contraction and initiates myocyte relaxation.

Several abnormal Ca^{2+} cycling may be observed in HF. A first condition is a diastolic leak of Ca^{2+} through altered RyR2 with the reduction of the Ca^{2+} content of the SR and then a reduction of Ca^{2+} that can be released during activation [26]. Some have attributed this mechanism to the hyper-phosphorylation of RyR2 at serine 2808 by phosphokinase A [27], others to the phosphorylation at serine 2814 by another enzyme, Ca^{2+}/calmodulin-dependent protein kinase II [28].

Another alteration of calcium metabolism is due to a loss of function of the SERCA2a pump with a reduction of Ca^{2+} content of cardiac SR. Phospholamban is SERCA2a-protein regulator. In the dephosphorylated state, phospholamban inhibits SERCA2a. Stimulation of b-adrenergic receptors normally causes the phosphorylation of phospholamban and thereby disinhibits SERCA2a, enhancing both cardiac contraction and relaxation. For the desensitization of myocardial b-receptors that occurs in HF, this mechanism provided by adrenergic stimulation may be reduced in this condition [29].

References

1. Sarnoff SJ, Berglund E. Ventricular function: I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation. 1954;9(5):706–18. https://doi.org/10.1161/01.CIR.9.5.706.
2. Araco M, Merlo M, Carr-White G, Sinagra G. Genetic bases of dilated cardiomyopathy. J Cardiovasc Med. 2017;18:123–30. https://doi.org/10.2459/JCM.0000000000000432.
3. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. 2012;366(7):619–28. https://doi.org/10.1056/NEJMoa1110186.
4. Roberts AM, Ware JS, Herman DS, Schafer S, Baksi J, Bick AJ, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. Sci Transl Med. 2015;7(270):270ra6. https://doi.org/10.1126/scitranslmed.3010134.
5. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest. 2013;123:19–26. https://doi.org/10.1172/JCI62862.
6. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, et al. Missense mutations in the rod domain of the Lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med. 1999;341:1715–24. https://doi.org/10.1056/NEJM199912023412302.
7. Taylor MRG, Fain PR, Sinagra G, Robinson ML, Robertson AD, Carniel E, et al., Familial Dilated Cardiomyopathy Registry Research Group. Natural history of dilated cardiomyopathy due to Lamin A/C gene mutations. J Am Coll Cardiol. 2003;41:771–80. https://doi.org/10.1016/S0735-1097(02)02954-6.
8. Zhou AX, Hartwig JH, Akyurek LM. Filamins in cell signaling, transcription and organ development. Trends Cell Biol. 2010;20:113–23. https://doi.org/10.1016/j.tcb.2009.12.001.
9. Garcia-Pavia P, Syrris P, Salas C, Evans A, Mirelis JG, Cobo-Marcos M, et al. Desmosomal protein gene mutations in patients with idiopathic dilated cardiomyopathy undergoing cardiac transplantation: a clinicopathological study. Heart. 2011;97:1744–52. https://doi.org/10.1136/hrt.2011.227967.
10. Brun F, Barnes CV, Sinagra G, Slavov D, Barbati G, Zhu X, et al., Familial Cardiomyopathy Registry. Titin and desmosomal genes in the natural history of arrhythmogenic right ventricular cardiomyopathy. J Med Genet. 2014;51:669–76. https://doi.org/10.1136/jmedgenet-2014-102591.
11. McNair WP, Sinagra G, Taylor MRG, Di Lenarda A, Ferguson DA, Salcedo EE, et al., Familial Cardiomyopathy Registry Research Group. SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol. 2011;57:2160–68. https://doi.org/10.1016/j.jacc.2010.09.084.
12. Zaklyazminskaya E, Dzemeshkevich S. The role of mutations in the SCN5A gene in cardiomyopathies. Biochim Biophys Acta. 2016;1863(7 Pt B):1799–805. https://doi.org/10.1016/j.bbamcr.2016.02.014.
13. Li D, Parks SB, Kushner JD, Nauman D, Burgess D, Ludwigsen S, et al. Mutations of presenilin genes in dilated cardiomyopathy and heart failure. Am J Hum Genet. 2006;79:1030–9. https://doi.org/10.1086/509900.
14. Troncone L, Luciani M, Coggins M, Wilker EH, Ho C-Y, Codispoti KE, et al. Ab amyloid pathology affects the hearts of patients with Alzheimer's disease. J Am Coll Cardiol. 2016;68:2395–407. https://doi.org/10.1016/j.jacc.2016.08.073.
15. Johnson FL. Pathophysiology and etiology of heart failure. Cardiol Clin. 2014;32(1):9–19. https://doi.org/10.1016/j.ccl.2013.09.015.
16. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, et al. Decreased catecholamine sensitivity and β-adrenergic-receptor density in failing human hearts. N Engl J Med. 1982;307:205–11. https://doi.org/10.1056/NEJM198207223070401.
17. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med. 1999;341(8):577–85. https://doi.org/10.1056/NEJM199908193410806.

18. McEwan PE, Gray GA, Sherry L, Webb DJ, Kenyon CJ. Differential effects of angiotensin II on cardiac cell proliferation and intramyocardial perivascular fibrosis in vivo. Circulation. 1998;98:2765–73. https://doi.org/10.1161/01.CIR.98.24.2765.
19. Liu Y, Leri A, Li B, Wang X, Cheng W, Kajstura J, et al. Angiotensin II stimulation in vitro induces hypertrophy of normal and postinfarcted ventricular myocytes. Circ Res. 1998;82:1145–59. https://doi.org/10.1161/01.RES.82.11.1145.
20. Zannad F, Dousset B, Alla F. Treatment of congestive heart failure: interfering the aldosterone-cardiac extracellular matrix relationship. Hypertension. 2001;38:1227–32. https://doi.org/10.1161/hy1101.099484.
21. Wang TJ, Larson MG, Benjamin EJ, Siwik DA, Safa R, Guo C-Y, et al. Clinical and echocardiographic correlates of plasma procollagen type III amino-terminal peptide levels in the community. Am Heart J. 2007;154:291–7. https://doi.org/10.1016/j.ahj.2007.04.006.
22. Shalitin N, Schlesinger H, Levy MJ, Kessler E, Kessler-Icekson G. Expression of procollagen C-proteinase enhancer in cultured rat heart fibroblasts: evidence for co-regulation with type I collagen. J Cell Biochem. 2003;90:397–407. https://doi.org/10.1002/jcb.10646.
23. Shi J, Dai W, Hale SL, Brown DA, Wang M, Han X, et al. Bendavia restores mitochondrial energy metabolism gene expression and suppresses cardiac fibrosis in the border zone of the infarcted heart. Life Sci. 2015;141:170–8. https://doi.org/10.1016/j.lfs.2015.09.022.
24. Nural-Guvener H, Zakharova L, Feehery L, Sljukic S, Gaballa M. Anti-fibrotic effects of class I HDAC inhibitor, mocetinostat is associated with IL-6/Stat3 signaling in ischemic heart failure. Int J Mol Sci. 2015;16:11482–99. https://doi.org/10.3390/ijms160511482.
25. Sanchis L, Andrea R, Falces C, Llopis J, Morales-Ruiz M, Lopez-Sobrino T, et al. Prognosis of new-onset heart failure outpatients and collagen biomarkers. Eur J Clin Investig. 2015;45:842–9. https://doi.org/10.1111/eci.12479.
26. Belevych AE, Terentyev D, Terentyeva R, Nishijima Y, Sridhar A, Hamlin RL, et al. The relationship between arrhythmogenesis and impaired contractility in heart failure: role of altered ryanodine receptor function. Cardiovasc Res. 2011;90:493–502. https://doi.org/10.1093/cvr/cvr025.
27. Shan J, Betzenhauser MJ, Kushnir A, Reiken S, Meli AC, Wronska A, et al. Role of chronic ryanodine receptor phosphorylation in heart failure and beta-adrenergic receptor blockade in mice. J Clin Invest. 2010;120:4375–87. https://doi.org/10.1172/JCI37649.
28. Respress JL, van Oort RJ, Li N, Rolim N, Dixit SS, DeAlmeida A, et al. Role of RyR2 phosphorylation at S2814 during heart failure progression. Circ Res. 2012;110:1474–83. https://doi.org/10.1161/CIRCRESAHA.112.268094.
29. El-Armouche A, Eschenhagen T. β-adrenergic stimulation and myocardial function in the failing heart. Heart Fail Rev. 2009;14:225–41. https://doi.org/10.1007/s10741-008-9132-8.