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Review

Changes of calcium cycling in HFrEF and HFpEF☆

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ABSTRACT

Dysfunctions of calcium cycling occur in heart failure with reduced and preserved ejection fraction (HFrEF and HFpEF). HFrEF and HFpEF showed Ca^{2+} leakage at diastole. The compensation of Na^{+}/Ca^{2+} exchanger and the decrease of T-tubule density reduces cytoplasmic Ca^{2+} concentration in HFrEF and impairs systolic function. In contrast, HFpEF has the increase of cytoplasmic Ca^{2+} concentration and diastolic dysfunctions. The decrease of mitochondrial Ca^{2+} concentration weakens myocardial contractility in HFrEF while the increased concentration retains the contractility in HFpEF. Here, the changes of calcium cycling in HFrEF and HFpEF are summarized and the possibility of relevant therapeutic targets is discussed.

1. Introduction

Heart failure (HF) is a complex clinical syndrome characterized by systolic or diastolic dysfunctions [1–3], which leads to a decrease in the pumping capacity of the heart. Heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) are two major heart failures (HF) [4,5]. In comparison with HFrEF, HFpEF shows diastolic dysfunction, myocardial hypertrophy and interstitial fibrosis and has heterogenous pathogenesis factors of type 2 diabetes, obesity, hypertension and so on [5–8].

Myocardial calcium is cycling through the synergism of calcium channel, ATPase pump, transporter and calcium binding protein [9]. There are cytoplasmic-sarcoplasmic reticulum (SR) calcium cycling and mitochondrial calcium cycling, which are of importance in the progression of HFrEF and HFpEF. This review summarizes changes of calcium cycling in HFrEF and HFpEF and shows relevant therapeutic targets.

2. Calcium cycling

2.1. Cytoplasmic-SR calcium cycling

SR mainly relies on ryanodine receptor 2 (RyR2) to release Ca^{2+} into the cytoplasm to activate the excitation-contraction coupling (ECC) [10]. At the end of systole, sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) (Ca^{2+}-ATPase 2A) is activated and reuptakes calcium [9]. S100 calcium binding protein A1 (S100A1), an important Ca^{2+} binding protein, exists in SR, sarcomere and mitochondria [9]. S100A1 increases the release of Ca^{2+} in systole and enhances the closure of RyR2 in diastole to prevent calcium leakage as well as increases the activity of SERCA2a in diastole and promotes Ca^{2+} uptake [11]. S100A1 deletion attenuates cardiac contractility and Ca^{2+} processing ability [12].

2.2. Mitochondrial calcium cycling

Mitochondrial calcium participates in tricarboxylic acid cycle, promotes ATP production, and adapts to higher energy requirements [13]. Mitochondrial calcium overload can lead to mitochondrial swelling, increased oxidative stress, mitochondrial membrane potential collapse, ATP production damage, permeability transition pore opening and so on [14,15].

Mitochondrial calcium uptake from cytoplasm mainly depends on mitochondrial calcium uniporter (MCU) complex [16], which consists of 4 MCU, 4 EMRE, 1 MICU1, 1 MICU2 and 1 MICU3 [17–20]. Mitochondrial calcium uptake is inhibited after MCU knockout [21,22]. MCU has low affinity for Ca^{2+} and high ability to transport Ca^{2+}, which leads to an S-shaped relationship between mitochondrial Ca^{2+} uptake and cytoplasmic Ca^{2+} concentration [23]. Hence, MCU can rapidly absorb Ca^{2+} during the exciting period (cardiac systole), and prevent Ca^{2+} uptake in

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the resting period (cardiac diastole). For mitochondrial calcium release, there are two major pathways: Na^+ dependent pathway (mitochondrial Na^+/Ca^{2+} exchanger, (NCLX)) and Na^+ independent pathway (Ca^{2+}/H^+ exchanger) [24]. The releasing rate of Na^+ dependent pathway is slightly higher than that of Na^+ independent pathway [24,25].

Mitochondria exchange Ca^{2+} directly with the SR. The mitochondrial-associated endoplasmic reticulum membranes (MAMs) [26] has the width of 10–50 nm [27]. The RyR2 and Ca^{2+} channels on the outer mitochondrial membrane (voltage-dependent anion selective channel (VDAC)) regulate the SR-mitochondrial calcium cycling [28]. The impaired interaction between SR and mitochondria reduces ATP production and activates apoptotic pathways [29].

3. Cytoplasmic-SR calcium cycling in HFrEF and HFpEF

3.1. Cytoplasmic-SR calcium cycling in HFrEF

In HFrEF, both systolic and diastolic dysfunctions are accompanied by calcium cycling dysfunctions. Impaired systolic SR Ca^{2+} release is closely related to myocardial T-tubules, e.g., the density of T-tubules decreases and the distance to SR increases in HFrEF rats [30,31]. The decrease of SR receiving excitatory signals can result in slow Ca^{2+} release and weak myocardial contractility. Moreover, calcium binding proteins (Triadin and Junctin) form complexes with RyR2 to regulate Ca^{2+} release. The reduced expression of Triadin and Junctin weaken the Ca^{2+} release impairing myocardial contractility in HFrEF patients [9]. On the other hand, the increase of cytoplasmic Ca^{2+} concentration is associated with the weakening of SR calcium uptake and calcium leakage at diastole. The decreased expression of SERCA2a reduces the diastolic SR Ca^{2+} uptake in HFrEF patients and animals [32]. The overexpression of SERCA enhances the cardiac function and prevents the occurrence of heart failure [32]. SERCA2a activity is mainly regulated by phosphoprotein (PLN) and the decreased ratio of SERCA2a to PLN results in a decrease in SERCA2a activity in HFrEF [9].

The abnormal phosphorylation of RyR2 results in an increase of Ca^{2+} leakage at diastole in HFrEF [33–36]. PKA and CaMKII phosphorylate RyR2 Ser 2808 and separated FK506 binding protein (FKBP12.6) from RyR2 to cause calcium leakage [37]. Inhibition of RyR2 Ser 2808 phosphorylation limits RyR2 dissociation from FKBP12.6 and calcium leakage [38,39]. Ser 2030 is also a target of PKA [40]. Moreover, the up-regulated expression of nitric oxide synthase (NOS), xanthine oxidase and NADPH oxidase (NOX) increase ROS level and oxidize RyR2 and cause calcium leakage [41]. To alleviate calcium leakage, the up-regulated Na^+/Ca^{2+} exchanger (NCX) expression promotes the release of Ca^{2+} in the cytoplasm at diastole [42].

3.2. Cytoplasmic-SR calcium cycling in HFpEF

In comparison with HFrEF, the increased density of T-tubules [30] promotes RyR2 Ca^{2+} release at systole in the myocardium of HFpEF patients [43]. This compensates for the increase of myocardial stiffness and avoids systolic impairments in a short term [44]. However, high Ca^{2+} concentration can induce myocardial hypertrophy in a long term, which could lead to subsequent decompensation. On the other hand, cytoplasmic Ca^{2+} concentration is increased and Ca^{2+} transient is disordered at diastole given the reduction of SR Ca^{2+} uptake and calcium leakage [45]. The reduction of SR Ca^{2+} uptake may be caused by the decreased SERCA2a/PLN ratio [46] despite no obvious abnormality in hypertensive-induced HFpEF [30]. The Ca^{2+} leakage depends on the phosphorylation of RyR2 Ser 2808 by PKA [44], but not CaMKII and the oxidation of RyR2 [30,47,48]. High Ca^{2+} concentration activates calcineurin NFAT, CaMKII histone deacetylase and other pathways to induce cardiac hypertrophy as well as continuously activates ECC to inhibit the relaxation of myocardial fibers resulting in the diastolic dysfunction.

The RyR2 activation pathways in HFrEF are more abundant than those in HFpEF, making them easier to activate, which is beneficial to increase myocardial contractility during systole and compensate for the decrease in cardiac contractility caused by HFrEF. This denotes that RyR2 conformations are inconsistent between HFpEF and HFrEF and RyR2 exposes more activation sites in HFrEF, which can be proved by the following analysis of protein structure. The conformational change may be beneficial for the treatment of muscle fiber diseases such as muscle weakness.

4. Mitochondrial calcium cycling in HFrEF and HFpEF

4.1. Mitochondrial calcium cycling in HFrEF

Because of the decreased Ca^{2+} uptake and the increased Ca^{2+} release, a reduction of mitochondrial Ca^{2+} concentration increases reactive oxygen species (ROS) production, impairs myocardial energy supply, and lowers myocardial contractility in HFrEF [49,50]. The overexpression of MCU could increase Ca^{2+} uptake to increase mitochondrial Ca^{2+} concentration and further reduce RyR2 oxidation and ROS production [51]. The elevated activity of NCLX, however, accelerates mitochondrial Ca^{2+} release and reduces mitochondrial Ca^{2+} concentration [49].

On the other hand, SR and mitochondria exchange Ca^{2+} directly through MAMs. The expression of MAMs related proteins (inositol 1,4,5-trisphosphate receptor type 2 (IP3r2), phosphofurin acidic cluster sorting protein 2 (PACS-2)) is decreased, the structure is destroyed and the number is reduced in HFrEF mice, which reduce the Ca^{2+} release of SR to mitochondria and weaken myocardial contractility [52]. Myocardial specific knockout of MAMs related protein (FUN14 domain containing 1, Fundc1) shows similar symptoms to HFrEF [52].

4.2. Mitochondrial calcium cycling in HFpEF

In contrast to HFrEF, there is an increase of mitochondrial Ca^{2+} concentration in HFpEF, which enhances mitochondrial function in a short term, but could open permeability transition pore to induce cardiomyocyte apoptosis in a long term [53]. Accordingly, there is no significant change in MCU expression [54]. The shorter distance between SR and mitochondria, the wider width of the junction, and the tighter MAMs are found in HFpEF mice with a high-fat and high sugar diet inducing diabetic cardiomyopathy [55]. Moreover, the expression of VDAC1, RyR2 and SERCA2 has neglectable changes, and the expression of mitofusin-2 is decreased. This denotes the changed shape and size of MAMs. In general, diabetic cardiomyopathy shows strong systolic dysfunctions, which is not the only feature of HFpEF [56]. Therefore, it is still required to investigate the role of MAMs in a more real animal model of HFpEF.

The reduction of various structural proteins in MAM leads to a decrease in the proportion of MAM in HFrEF. There is a close relationship between MAM and mitochondrial fusion and fission. Mitochondrial fission increased in HFrEF, showing fragmentation. Excessively small mitochondria result in a decrease in MAM. There is an increase in mitochondrial fusion in HFpEF, and larger mitochondria facilitate the formation of MAM, leading to an increase in MAM.

5. Treatment modalities targeting calcium cycling

5.1. Targeting cytoplasmic-SR calcium cycling

Targeting cytoplasmic-SR calcium cycling has attracted attention to the treatment of HF, which mainly focuses on regulation of SR Ca^{2+} uptake and calcium leakage at present. Overexpressing SERCA2a improves HF symptoms, reduces cardiovascular events after 12 months, and shortens the length of hospital stay [57]. The three-year follow-up shows the significantly decreased incidence of clinical events [58]. In animal models, inhibiting PLN and increasing SERCA2a activity inhibit the progression of HF [59,60]. Overexpression of small ubiquitin like modifier 1 (SUMO1) can enhance the activity and stability of SERCA2a to

alleviate HF [61]. On the other hand, FKBP12.6 is a RyR2 regulatory protein that enhances RyR2 stability. The HF progression is limited by increasing the interaction of RyR2 and FKBP12.6 with compounds such as Rycals (K201 derivatives) [62]. Moreover, overexpression of S100A1 improves HF by interacting with RyR2 and SERCA2a. Hence, SERCA2a and RyR2 are good therapeutic targets.

5.2. Targeting mitochondrial calcium cycling

Mitochondrial calcium cycling plays an important role. Overexpression of MCU increases the level of mitochondrial Ca^{2+}, alleviates SR Ca^{2+} leakage, and improves the HFrEF phenotype [63]. However, MCU has negligible effects on HFpEF. Because of its important role in calcium cycling and mitochondrial dynamics, MAMs can be a potential therapeutic target for HF, which needs to be confirmed in future studies. Our group has recently found that PTEN induced kinase 1 (PINK1) could phosphorylate dynamin 1 like^{S616} (Drp1^{S616}) to improve mitochondrial fission and relieve mitochondrial dysfunctions, which highlights potential treatments of HFpEF [64].

6. Summary and prospect

Calcium cycling shows different changes between HFrEF and HFpEF, as shown in Fig. 1. HFrEF has strong contractile dysfunctions relevant to abnormal SR Ca^{2+} release caused by the increased NCX expression and decreased T-tubule density and HFpEF has strong diastolic dysfunctions associated with high cytoplasmic Ca^{2+} concentration due to the unchanged NCX and increased density of T-tubules albeit they have decreased SERCA2a activity and RyR2 hyperactivation for leakage of SR Ca^{2+} at diastole. In the mitochondrial calcium cycling, the reduction of MCU activity and MAMs results in the decreased mitochondrial Ca^{2+} concentration and myocardial contractility in HFrEF while mitochondrial Ca^{2+} concentration increases in HFpEF.

Overall, calcium cycling is closely related to the occurrence and development of heart failure, but there are limited studies on mitochondrial calcium cycling, especially for MAM. MAM is not only an important part of mitochondrial calcium cycling, but also participates in the regulation of mitochondrial dynamics. This suggests that there may be a close relationship between mitochondrial dynamics and calcium cycling, which will be a research direction of interest in the future.

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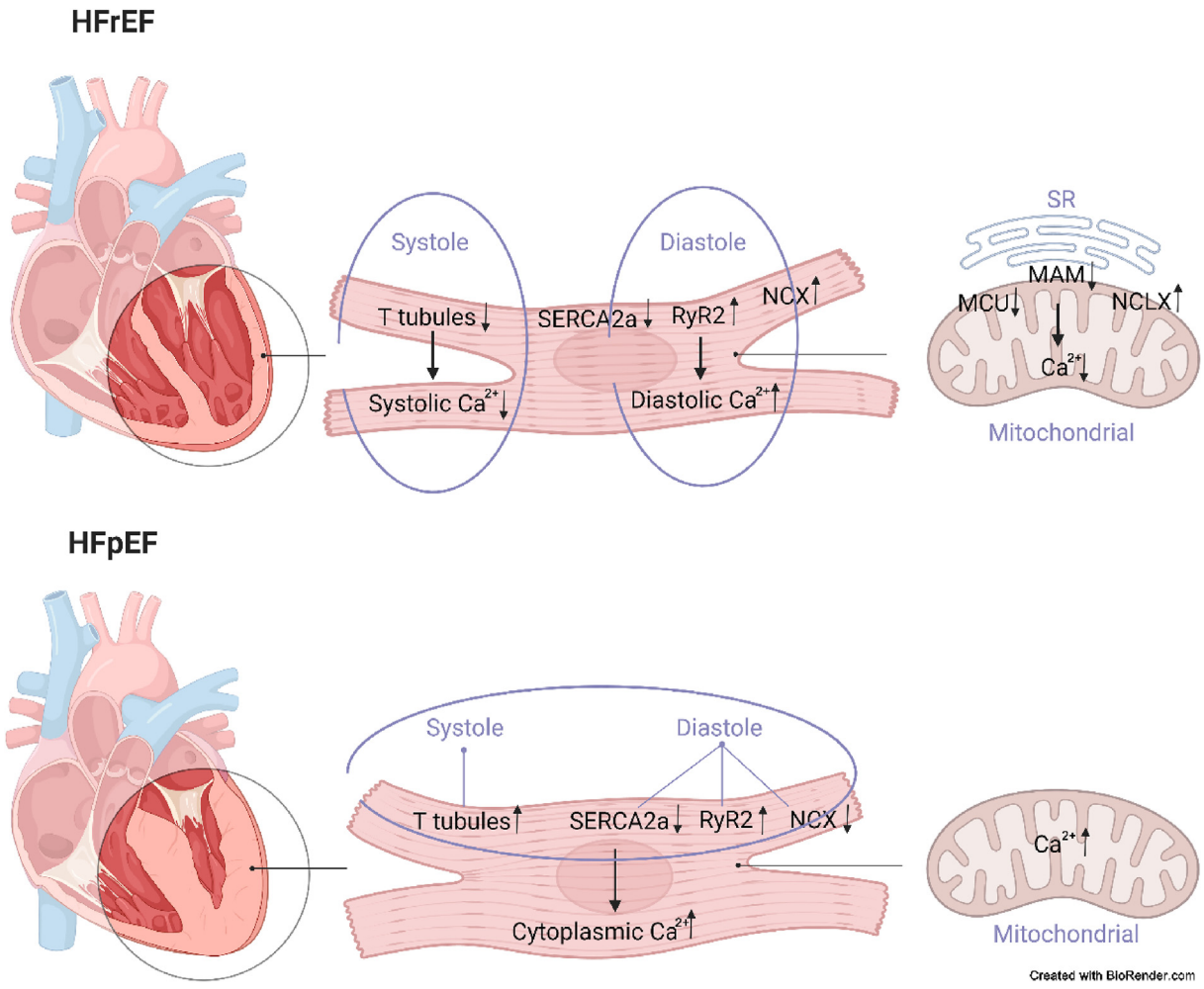

Fig. 1. Calcium cycling in HFrEF and HFpEF. Both HFrEF and HFpEF exhibit RyR2 hyperactivation and reduced SERCA2a activity, resulting in Ca^{2+} leakage during diastole. HFrEF shows increased NCX expression and decreased T-tubule density, resulting in decreased cytoplasmic Ca^{2+} during systole. In contrast, HFpEF shows decreased NCX expression and increased T-tubule density, resulting in increased cytoplasmic Ca^{2+}. In the mitochondrial calcium cycling, MCU activity and MAMs content decreased in HFrEF, result in decreased mitochondrial Ca^{2+}. In contrast, mitochondrial Ca^{2+} increases in HFpEF.

Conflicts of interest

The authors declare no conflict of interest.

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