Cardiac resynchronization therapy – beneficial alterations observed at the molecular level – a review

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Abstract

Cardiac resynchronization therapy (CRT) is a relatively new option for the treatment of heart failure patients with intraventricular conduction disturbances (i.e. QRS wider than 130 ms), especially with dyssynchronous heart failure (left bundle branch block). From a pathophysiological point of view it restores simultaneous depolarization of heart ventricles and optimizes the heart function, which provides clinical benefits. At the molecular level, CRT leads to restoration of disturbances caused during dyssynchronous heart failure development and progression, related to electrophysiology (potassium and sodium currents, connexin-43 localization), structure (α-actinin organization, α-myosin heavy chain protein expression), apoptosis, oxygen consumption and inflammation. One of the most important benefits of CRT is its ability to increase the efficiency of heart work without enhancement of oxygen consumption. In this review we summarize the principal alterations caused by CRT at the molecular level.

Introduction

Cardiac resynchronization therapy (CRT) is a subtype of pacing therapy in which an additional ventricular lead is placed in the coronary sinus, evoking, together with the right ventricular lead, a simultaneous depolarization between the left and right ventricle. This therapy aims to restore the physiological way of depolarization and cardiac muscle contraction. According to the European Society of Cardiology Guidelines, the indications for CRT include chronic congestive heart failure with left ventricular ejection fraction (LVEF) lower than 35% and with QRS duration longer than 130 ms. Moreover, CRT is recommended in congestive heart failure (CHF) patients with decreased LVEF (≤ 35%), left bundle branch block (LBBB) and QRS duration longer than 150 ms[1]. The large randomized clinical trial MADIT-CRT has provided evidence of beneficial clinical effects of CRT – CHF patients randomized for ICD-CRT presented a 41% decrease in risk of heart failure events and a significant reduction in the primary end-point (heart failure event and overall mortality) in comparison with the ICD only group (17.2% vs 25.3% for primary end-point)[2]. It is necessary to point out that long-term effects of cardiac resyn-

chronization therapy rely on molecular changes caused by it. In this brief review we aim to describe alterations evoked by CRT at the cellular and molecular level. However, not every patient benefits from this therapy – some patients are non-responders (approximately 30%) and the differences between non-responders and responders are also informative for the analysis of the molecular response to CRT[3].

Electrophysiological alterations

The main sign observed in heart failure at the cellular level is prolonged action potential (AP) caused by disturbance in the potassium and sodium ion currents and associated with predisposition to arrhythmia.[4, 5] Additionally, conduction velocity is slower in epicardial regions compared to endocardial regions (the situation opposite to a healthy tissue), while action potential duration decreases in late depolarizing areas and increases in early depolarizing areas. Such heterogeneity of AP duration is highly arrhythmogenic. These changes are partially attributed to the alterations of gap junctions' connexin-43 (Cx43) protein expression and distribution[6]. At the electrophysiological level, in dyssynchronous heart failure (DHF) many changes such as reduction of repolarizing K+ currents, late Na+ current and changes in Ca2+ currents are also observed[6, 7]. Most of the abovementioned pathologies can be restored by using CRT, thus normalizing AP[4, 5, 7, 8]. However, the CRT does not succeed in reversing all the effects caused by DHF, for instance downregulation of Ito, mRNA Kv4.3 and KChIP2, which do not normalize even when CRT is applied[4].

In reference to the potassium channels, DHF causes reduction of inward rectifier IK1 and delayed rectifier IK currents that are partially restored by the CRT. Calcium homeostasis is also altered in dyssynchronous heart – sarcoplasmic reticulum Ca2+-ATPase (SERCA 2a) and ryanodine receptor RyR2 expression is reduced, whereas Na+/Ca2+ exchanger (NCX) expression is increased. In human heart, ICa-L channel density is mostly unchanged in spite of heart failure. Interestingly, an experiment in a canine model revealed that ICa-L density is reduced in myocardium from the lateral wall of the left ventricle and increased in myocardium from the anterior wall. In those animals the CRT restored peak current density and eliminated heterogeneity without changing SERCA2a, NCX and RyR2 expression at the mRNA level[8, 9].

In contrast to the ionic currents mentioned above, DHF increases the late INa-L sodium current. As a result, the cytosol is overloaded with sodium ions, which leads to prolonged AP and early afterdepolarisations that may contribute to arrhythmia and prolonged repolarisation[4, 10]. Studies show that increased late sodium current is caused by higher activity of CaMKII, which inhibits the inactivation of sodium channels. CRT restores the proper level of INa-L current intensity partly by normalizing the activity of CaMKII, reducing its autophosphorylation[10].

As a result of DHF and after myocardial infarction, connexin-43 is lateralized in the cardiomyocytes of the left ventricle. This change causes a decrease in a velocity of AP conduction between cardiomyocytes and affects physiological variability of repolarization of individual cells, which may favour the formation of re-entry loops – an arrythmia substrate. In experiments on dogs, lateralisation and reduction of Cx43 expression was connected with decreased conduction in His-Purkinje fibres[11]. The mechanism of this change might involve renin-angiotensin signalling[12]. The use of CRT regulates the activity of protein kinase B, which phosphorylates Cx43, restoring proper communication between myocardium cells[13]. The aforementioned aspects are illustrated in Figure 1.

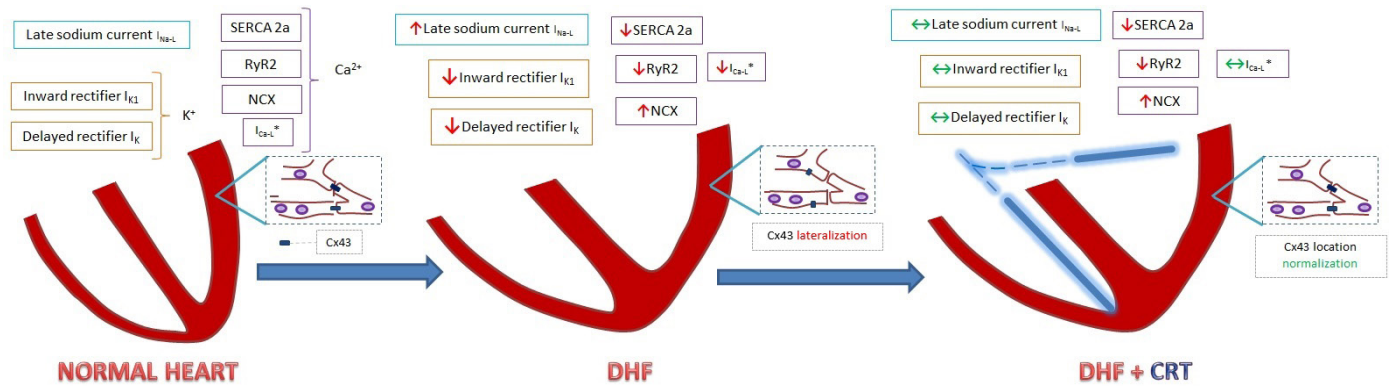

Figure 1. Electrophysiological and associated molecular alterations developed during dyssynchronous heart failure progression and reaction after CRT implementation. ↑ - increase; ↓ - decrease; ←→ - normalization (partial or complete); * - in canine model

Structural alterations

During the development of dyssynchronous heart failure many structural and ultrastructural alterations are observed. However, these alterations can be partially reversed by CRT. Frequent changes in dyssynchronous heart failure (DHF) occur in peripheral parts of the myocardium, leading to heterogeneous change in the expression of genes encoding structural and channel proteins[7, 13]. Lesions in the cardiomyocytes may affect the cytoskeleton, which is responsible for keeping sarcomeres in the appropriate position. Increased haemodynamic forces that act upon myocardial cells cause the alteration of ventricular architecture due to changes in cardiomyocytes ultrastructure and extracellular matrix modifications. In a normal heart, α-actinin proteins construct regular, parallel, transverse

sheets that forms Z-discs between sarcomeres, whereas in heart failure (especially dyssynchronous) special regularity of α-actinin distribution is disturbed and longitudinal α-actinin depositions are formed[13, 14]. According to Kirk et al. in DHF a poor myofilament response to calcium is observed, which is likely related to the deactivation of glycogen synthase kinase-3β (GSK-3β) and dephosphorylation of Z-disk and M-band proteins[5, 15]. In heart failure patients with LBBB the expression of genes encoding motor proteins regulating sarcomeres' contraction (especially α-myosin heavy chain, α-MHC) is decreased. All aforementioned disturbances are normalized after using CRT. Importantly, the study by Vanderheyden et al. showed that CRT restores the expression of α-MHC only in the "responders" and not in the "non-responders" to cardiac resynchronization[16].

In response to the presence of mechanical stimuli resulting from excessive cardiac ventricular stretching the myofibroblasts produce extracellular matrix (ECM) and contribute to fibrosis in order to counteract excessive strain[17, 18]. This is related to the imbalance between matrix metalloproteinases (MMPs) and their inhibitors, which is associated with cardiac dilation and stiffness. Restoring the synchronous heart rate with CRT normalizes the stress in the ventricular wall, allowing for reverse remodelling, which manifests itself in changes in the levels of ECM regulatory factors (MMP-9, galectin-3, prokol-3NT)[19]. Aforementioned structural alterations during dyssynchronous heart failure progression and reaction to CRT are illustrated in Figure 2.

In summary, myocardial hypertrophy in dyssynchronous heart failure is caused by excessive systolic stressors and subsequent excessive secretion of neurohormones and growth factors, which lead to an increase in the amount of myofibrils without changes in the strength of the muscle contractions[15]. There may also be a decrease in the expression of α-MHC[11]. CRT improves systolic properties of the left ventricle and contributes to retrograde remodelling of the heart by reduction of fibrosis, stabilization of paracrine hormone levels and restoration of α-MHC expression[11].

In heart failure, in addition to hypertrophy and fibrosis, cardiomyocytes also undergo apoptosis, which leads to further changes in the anatomical structure of the heart. Both in humans and animals, it has been confirmed that CRT inhibits apoptosis caused by dyssynchronous heart failure[6]. CRT leads to a decrease in the plasma concentration of Anx5, a plasma marker of apoptotic processes[11, 22]. The overexpression of Anx5 is correlated with the decrease of antiapoptotic proteins' (like Bcl-2) activity, increased permeability of mitochondrial membrane and activation of caspase-3 – an executor of the apoptotic process. Gong et al. determined other mitochondrial proteins leading to apoptosis as a result of heart failure (CAPN1, ATP2A1, Anx6), concentrations of which also decrease after CRT implementation. One of them (CAPN1) is linked to the regulation of calcium levels in the myocardial cell and contributes to the disturbance of calcium homeostasis in cells in response to mitochondrial overload. CAPN1 also promotes degradation of sarcomeres and formation of autophagosomes[23]. Moreover,

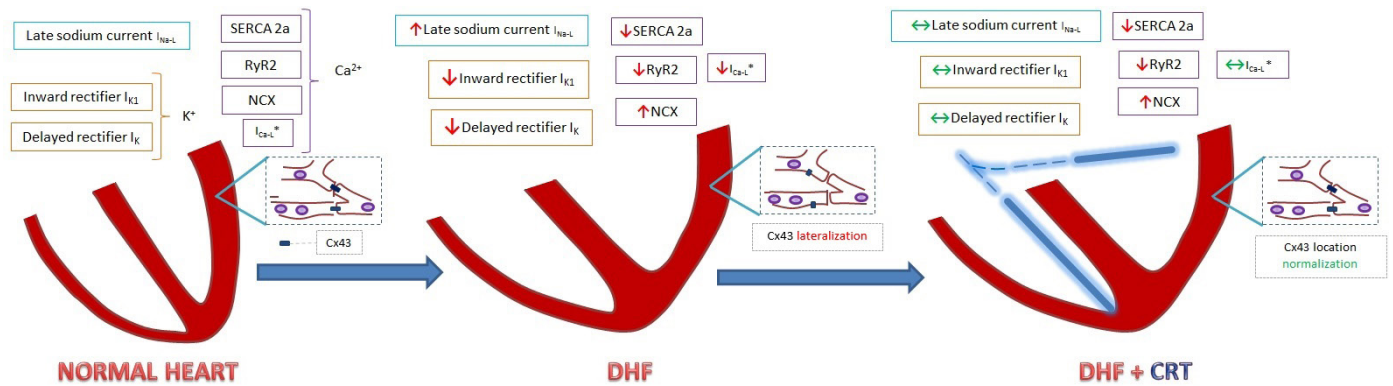

Figure 2. Structural and associated molecular alterations developed during dyssynchronous heart failure progression and reaction after CRT implementation. ↑ - increase; ↓ - decrease; ←→ - normalization (partial or complete)

In the process of heart remodelling associated with heart failure and response to cardiac resynchronization therapy the microRNA particles are also involved. Marfella et al. reported that 48 miRNAs are downregulated in heart failure patients in comparison with healthy subjects and an appropriate response to CRT results in the upregulation of expression of 19 miRNAs in comparison with baseline expression. Responders presented significantly higher expression of 5 miRNAs (miRNA-26b-5p, miRNA-145-5p, miRNA-92a-3p, miRNA-30e-5p, and miRNA-29a-3p) than non-responders[20]. Another study showed that miRNA-30d expression is increased in CRT responders compared with the non-responders and control group. miRNA-30d presents anti-apoptotic activity and promotes cardiomyocyte growth[21].

during DHF the kinases responding to cellular stress (MAPK, CaMKII, Akt) and activating apoptotic pathways are activated, which is reversed by CRT, which results in the promotion of anti-apoptotic pathways[9, 24].

Impact upon oxygen consumption

Therapies that improve cardiac efficiency while increasing oxygen consumption may have a detrimental effect in long-term use[25]. Therefore, treatment that enhances hemodynamic parameters without increase of energy demand is warranted. Positron emission tomography studies, both in the long term and early after initiation of CRT, have shown that an increase in cardiac efficiency is not accompanied by the enhancement of

oxygen consumption. However, changes are noticeable at the regional level. In the case of LBBB, the contraction of previously activated segments of the heart increases intraventricular pressure, so that late-activated lateral wall cardiomyocytes work harder and myocardial oxygen consumption in that region is elevated compared to the septum[26, 27]. Resynchronization of heart muscle and simultaneous contraction of the entire heart owing to the CRT make it possible to eliminate these differences, unify oxygen consumption between the segments and increase work efficiency[26, 28-31]. This contributes to reverse remodelling of the ventricles and supresses the asymmetry in hypertrophy resulting from LBBB[32]. Some studies have shown that CRT can even reduce the global energy cost of heart activity[25, 33]. Importantly, heart failure and CRT induce subcellular changes affecting energy management. Studies based on a canine model have shown that heart failure is associated with decline of ATPase activity and increase of mitochondrial basal oxygen consumption[24]. CRT alters the expression and post-translational modifications of mitochondrial enzymes involved in pyruvate metabolism, the Krebs cycle, and respiratory chain and increases the assembly of complex V of the ATP synthase β-subunit. These changes result in improved ATP synthetic capacity[34]. Another study showed that CRT reversed S-glutathionylation of the ATP synthase α-subunit that occurred in dyssynchronous heart failure and improved oxidative phosphorylation[35]. Apart from apoptosis, Anx5 overexpression during heart failure is also associated with reduced ATP availability. In turn, CRT has the ability to reduce annexin A5 plasma concentration in responders, which is associated with reverse LV remodelling and improvement of cardiac systolic function[22]. Abnormal expression of 128 proteins, including those located in mitochondria, was also reversed by CRT[23].

Impact upon inflammation

It is known that proinflammatory cytokines play an important role in pathogenesis of heart failure causing disturbance of contractility and promotion of ventricular remodelling[36]. One of the additional benefits of CRT is suppression of the immune response. Michelucci et al. in a study on 140 patients classified as NYHA III and IV with intraventricular dyssynchrony who underwent CRT observed that decrease of IL-6 and CRP concentration is linked to reverse remodelling and better clinical prognosis[37].

There are a number of studies where CRT reduces inflammatory reactions by decreasing concentrations of CRP, sTNFR-I, sTNFR-II, TNF-alfa, TGF-BETA1, IL-6, IL-1Beta, IL-8 and MCP-1,[38-44]. However, studies demonstrating unchanged levels of cytokines have also been reported, especially in reference to the non-responders[45]. In addition, CRT also depletes complement activation[46] and inhibits the response mediated by interleukin 17 (IL17) producing cells[47].

The mechanisms of these phenomena are not clearly understood. According to one of the theories, contractility of cardiac muscle with reduced wall tension attenuates local production of cytokines. However, modification of peripheral secretion of inflammatory factors is also possible[45].

Conclusion

CRT is an important and established treatment for patients with dyssynchronous heart failure. This therapy aiming to restore myocardial synchronization yields benefits at the molecular level. Further investigation may contribute to improved effectiveness of this treatment.

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