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Functional consequences of abnormal Cx43 expression in the heart ☆

Magda S.C. Fontes [a], Toon A.B. van Veen [a], Jacques M.T. de Bakker [a,b], Harold V.M. van Rijen [a,*]

[a] Department of Medical Physiology, University Medical Center, Utrecht, The Netherlands
[b] The Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

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ABSTRACT

The major gap junction protein expressed in the heart, connexin43 (Cx43), is highly remodeled in the diseased heart. Usually, Cx43 is down-regulated and heterogeneously redistributed to the lateral sides of cardiomyocytes. Reverse remodeling of the impaired Cx43 expression could restore normal cardiac function and normalize electrical stability. In this review, the reduced and heterogeneous Cx43 expression in the heart will be addressed in hypertrophic, dilated and ischemic cardiomyopathy together with its functional consequences of conduction velocity slowing, dispersed impulse conduction, its interaction with fibrosis and propensity to generate arrhythmias. Finally, different therapies are discussed. Treatments aimed to improve the Cx43 expression levels show new potentially anti-arrhythmic therapies during heart failure, but those in the context of acute ischemia can be anti-arrhythmogenic at the cost of larger infarct sizes. This article is part of a Special Issue entitled: The Communicating junctions, composition, structure and characteristics.

1. Introduction

The electrical activation pattern of the heart normally starts in the sinoatrial node (SAN) is then conducted along the atria, delayed in the atrioventricular node (AVN), proceeds through the atrioventricular conduction system and finally ends in the ventricles. Along this pathway, all myocytes are individually activated by intercellular currents that flow through gap junctions.

In the heart, 3 main gap junction proteins are found in the conductive and working myocardial cells: Connexin40 (Cx40), Connexin43 (Cx43), and Connexin45 (Cx45) (Fig. 1). Cx40 is expressed in atrial myocytes, in the AVN, His-bundle and ventricular conduction system [1–6]. Cx43 is by far the most abundant, and is extensively expressed between atrial and ventricular myocytes and to lower degree in parts of the ventricular conduction system [3,5,7–14]. The expression of Cx45 is restricted to the SAN, the AVN, His-bundle and ventricular conduction system [5,15–18].

Normally, gap junctions (Cx43) between ventricular myocytes are expressed in a polarized way. Gap junctions are mainly localized at intercalated disks (IDs) at the cell poles, and have relatively low density at lateral sides [12,13,19–22]. As a consequence, electrical conduction can propagate in both longitudinal and transverse directions. This conduction velocity (CV) is normally higher in the longitudinal than in the transverse direction, giving rise to the phenomenon of anisotropy [23,24].

Changes in cardiac workload, either by extrinsic factors, such as pressure or volume overload, or by intrinsic factors such as myocardial infarction or familial hypertrophic cardiomyopathy, generally induce hypertrophic growth of individual myocytes. The classic view is that hypertrophic growth of myocytes counteracts the increased wall tension (Laplace's law), and is therefore often called compensated hypertrophy [25,26]. Although called compensatory, a prolonged state of hypertrophy increases the risk for progression into heart failure (decompensated hypertrophy). Heart failure has a high morbidity and mortality, which is strongly determined by the high propensity of remodeled hearts to fatal ventricular tachyarrhythmias [27–33].

The cardiac remodeling process is governed by structural and electrical changes that decrease the electrical stability of the heart. A hallmark of the electrical changes with regard to impulse conduction is a change in electrical coupling due to abnormal expression of Cx43-constituted gap junctions. Cx43 protein expression is typically down-regulated and channels are often heterogeneously redistributed. This abnormal Cx43 expression is often associated with abnormal conduction and arrhythmias, although there seems to be a large reserve before reduced intercellular coupling becomes arrhythmogenic [34–36].

In previous reviews we focused on the structure, properties and knockout animal models of Cx43, while in the current review we will focus on Cx43 remodeling in hypertrophic, dilated and ischemic cardiomyopathies and their functional consequences, both in human and animal studies (Table 1) [37–39].

Abbreviations: BZ, border zone; CV, conduction velocity; Cx43, connexin43; DCM, dilated cardiomyopathy; ERP, effective refractory period; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; IDs, intercalated disks; LV, left ventricle

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* Corresponding author at: Division of Heart & Lungs Department of Medical Physiology, University Medical Center Utrecht, Yalelaan 50, 3584 CM Utrecht, The Netherlands. Tel.: +31 302538900; fax: +31 302539036.
E-mail address: h.v.m.vanrijen@umcutrecht.nl (H.V.M. van Rijen).

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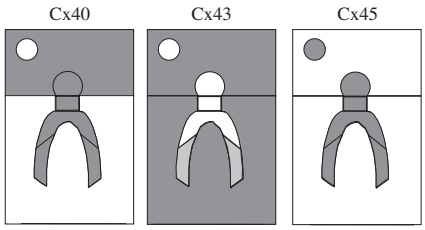

Fig. 1. Summary expression patterns of Cx40, Cx43 and Cx45 in the mammalian heart (redrawn after [132]).

2. Electrical coupling, impulse conduction and arrhythmias

Electrical coupling is essential for normal impulse propagation through the heart, together with proper excitability of the cardiomyocytes and normal tissue architecture. Reduced electrical coupling can increase the propensity for arrhythmias by facilitating reentry activity. 'Circulating excitation' was first recognized by George Mines as a possible mechanism of arrhythmias [40] and he already showed that: 'The circumstances under which the phenomenon made its appearance were such as to produce the favourable conditions of slow conduction and short refractory period'. The relation between CV, the effective refractory period (ERP) and reentry was later captured in the term 'wavelength' (λ) which is the distance of the impulse traveled during the refractory period ($\lambda = CV \times ERP$ [41]). Usually, λ is too large to facilitate reentry. In a mouse heart, e.g., CV is ~40 cm/s and ERP is ~50 ms [42], resulting in a λ of 2 cm, which is too large to fit on a mouse heart. Conditions that shorten the refractory period or decrease CV will result in a shorter λ, which may fit more easily on the heart, thus increasing the propensity for reentrant arrhythmias. Conversely, conditions that prolong refractoriness or increase CV are expected to prolong the wavelength and reduce arrhythmogeneity [41,43].

Reduced expression of Cx43, leading to reduced intercellular coupling is usually associated with reduced CV. However, the relationship between electrical coupling and CV is not linear [44], and solid reductions in Cx43 expression are required for reduction of CV. Mice heterozygously deficient for Cx43 showed 50% reduction in Cx43 expression that was associated in some studies with reduced CV, but in others with no effect in the CV [42,45–49]. Reduction of about 90% in Cx43 expression resulted in about 50% decrease in the CV [42,50]. While 50% reduction in Cx43 may lead to some conduction slowing, high levels of electrical uncoupling are needed to increase arrhythmogeneity. Abnormal tissue architecture, e.g. due to increase of collagen deposition (fibrosis), may have synergistic effects together with reduced Cx43 expression and lead to conduction slowing as reviewed by [51].

3. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is categorized as concentric hypertrophy, with thickening of the left ventricular (LV) wall without a significant dilation of the LV cavity, and is also characterized by cardiomyocyte hypertrophy, myofibrillar disarray, and fibrosis (Fig. 2) [27,52]. HCM is usually associated with pressure overload due to aortic stenosis or chronic hypertension [27].

In LV biopsies of HCM patients with valvular aortic stenosis, Cx43 was subject to a remodeling process between compensated and decompensated hypertrophy. As mentioned above, compensated hypertrophy reflects proper working myocardium (e.g. ejection fraction > 50%), which may progress to a failing myocardium, decompensated hypertrophy (e.g. ejection fraction < 30%). While compensated hypertrophy had increased levels and increased lateral Cx43 expression, decompensated hypertrophy revealed a heterogeneous reduction of Cx43 [53]. In other human studies, besides myofiber disarray, a Cx43 redistribution from IDs to the lateral sides of cardiomyocytes, resulting in reduced Cx43 at the IDs, was reported [21,54,55]. The reduction of Cx43 was not associated with a change in the number of IDs, although they presented an abnormal organization as well as abnormal desmosome organization [55]. In contrast with the above observation of a Cx43 down-regulation, an increase of Cx43 expression levels in LV biopsies from HCM patients was recently reported for the first time [54].

Some animal models of HCM showed changes in Cx43 expression similar to that found in humans. A study of transgenic rabbits bearing a mutation in Troponin I that causes HCM in humans, revealed typical HCM characteristics such as cardiomyocyte disarray, fibrosis, and Cx43 disorganization. This disorganization was reflected by a heterogeneous redistribution of Cx43 together with increased levels and increased phosphorylation of Cx43. In these transgenic rabbits no ECG abnormalities were detected, except an altered repolarization phase. The heterogeneous expression of Cx43 did not lead to enhanced arrhythmogeneity, perhaps due to the overall increased levels of Cx43 [56]. Cx43 up-regulation was also detected in another rabbit model of HCM (β-myosin heavy chain-Q403), but only in the midmyocardium. No effect on action potential duration, conduction velocities and anisotropy was detected [57].

In a guinea pig model with chronic aortic stenosis a reduction in the expression of Cx43, remodeling of IDs and alteration in myocyte shape was observed after transition from compensated to decompensated LV hypertrophy [58].

Finally, a rat model of HCM (monocrotaline-induced pulmonary hypertension or pressure overload) showed, in both right and left ventricle, a normal distribution of desmoplakin in the IDs and normal levels of total Cx43, although there was redistribution of Cx43 from the IDs to the cytoplasm and lateral sides of myocytes, and increased dephosphorylated Cx43 [59–61]. Furthermore, measurements of CV in the right ventricle revealed a decrease in the longitudinal direction when compared with control, while transversal CV remained unchanged, resulting in reduced anisotropic ratio [59]. Reduced longitudinal CV probably resulted from reduced Cx43 at IDs, while unchanged transversal CV probably resulted from non-functional lateral Cx43, which may reflect the increase in dephosphorylation of Cx43. In another rat model of pressure overload by ascending aortic banding, a reduction in Cx43 expression, an increase in dephosphorylated Cx43 and a reduction in CV in the late stage of hypertrophy was found [62]. However, as described above in a human HCM study, in early stages of hypertrophy the typical increase of Cx43 was observed, but also an increase in phosphorylation of Cx43, and slowing of CV that was less severe than observed in the late stage. In this animal model of pressure overload it was possible to induce sustained ventricular tachyarrhythmia [62].

Reports from HCM patients and different animal models revealed an increase and lateralization of Cx43 together with slowing of CV in early, compensated stage of hypertrophy that was followed by a reduction of Cx43, resulting in development of arrhythmias.

4. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by eccentric hypertrophy, with thickening of the LV wall in conjunction with an increase in the diameter of the LV cavity (Fig. 2). It is usually associated with volume overload, as aortic or mitral valve regurgitation and anemia or as muscle dysfunction [27,29,63].

Left ventricular biopsies from patients with DCM showed heterogeneous down-regulation of Cx43 expression, with a greater loss in the IDs compared to the lateral sides [54,64,65]. In small areas of replacement fibrosis there was a redistribution of Cx43, whereas in areas distant from this region, Cx43 was normally distributed in the IDs [65]. Hearts from DCM patients who died suddenly also showed reduction and redistribution of Cx43 expression in both ventricles [66]. Since the control hearts used in this study were from patients without DCM, no

Table 1
Abnormal Cx43 expression in heart remodeling.

Cardiomyopathy	Origin	Cx43				Fibrosis	CV	Arrhythmias	Comments	References
		Expression	Phosphorylation	Distribution						
				Heterogeneous	Lateralized					
HCM	Human			↑	↑				Myofiber disarray, remodeling of IDs	[21]
		↑ LV (early stage) ↓ LV (late stage)		↑ LV	↑ LV (early stage)					[53]
		↓ LV								[55]
		↑ LV			↑ LV					[54]
	Rabbit	↑	↑	↑		↑		=	Cardiomyocyte disarray, altered repolarization phase	[56]
		↑ (Midmyocardial)					=		↑ LV transmural fiber rotation, normal APD	[133]
	Guinea Pig	↓ LV							Altered ventricular myocyte shape, remodeling of IDs	[58]
	Rat	↓ RV (IDs)		↑ RV			↓ CV_L =CV_T			[59]
		↓ LV		↑ LV	↑ LV					[60]
		=RV	↓ RV	↑ RV						[59–61]
		↑ (early stage) ↓ (late stage)	↑ (early stage) ↓ (late stage)			↑ (late stage)	↓ (early stage) ↓↓ (late stage)	↑	↑ APD	[62]
DCM	Human	↓		↑		=		↑		[67,68]
		↓		↑						[66]
		↓ LV		↑ LV						[64]
		↓ LV (distant from fibrosis)		↑ LV (areas of fibrosis)						[65]
		↓ LV		↑ LV						[54]
	Pig	↑ (early stage) ↓ (late stage)				↑ (late stage)			Expansion of cardiomyocytes myofilaments	[80]
	Dog	↓ LV	↓	↑ LV	↑ LV	=	↓	↑	↑ QRS interval No change in action potential upstroke velocity	[69]
		↓	↓		↑		↓			[75]
	Rabbit	↑								[81]
	Mouse	↓		↑	↑ LV		↓ Heterogeneous	= Regional conduction block	↑ QRS interval	[77]
		↓					↓			[78]
		=		↑ (VT+)		↑	↓ RV CV_L Heterogeneous	↑ (44%)	↓ Fractional shortening ↑ PQ, QT and QRS prolongation	[79]
ICM	Human	↓ (distant from BZ)		↑ (BZ) = (distant from BZ)	↑ (BZ)				Altered myocyte orientation and cell shape in BZ	[85,134]
							= CV_L ↓ CV_T		↑ Refractory period	[86]
		↓ LV			= LV				Change in cell size distribution	[55]
		↓ LV		↑ LV					↑ Cx40	[64]
		↓ (distant from BZ)		↑ (BZ) = (distant from BZ)						[65]
	Dog	↓				↑ (BZ)			Cardiomyocyte disarray	[96]
		↓	↓	↑						[87]
							= CV_L ↓ CV_T	↑		[100]
				↑	↑	↑ (BZ)		↑		[101]
	Pig						↓ Heterogeneous			[104]
	Rabbit	↓		↑						[88]
							↓			[89]
	Rat	=	↓							[90]
		↓			↑					[105]
		↓			↑					[106]

Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; ↑, increased; ↓, decreased; ↓↓, more decreased than ↓; =, unchanged; LV, left ventricle; RV, right ventricle; CV_L, longitudinal conduction velocity; CV_T, transversal conduction velocity; VT+, occurrence of ventricular tachycardia; BZ, border zone; ID, intercalated disk; APD, action potential duration.

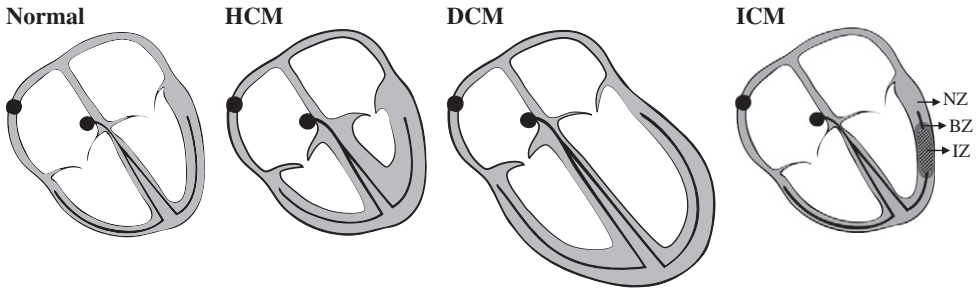

Fig. 2. Morphologic differences between normal and cardiomyopathic hearts. *From left to right*: normal, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and ischemic cardiomyopathy (ICM). In ICM a border zone (BZ) is present between the infarct zone (IZ) and the normal zone (NZ).

correlation could be made between reduction of Cx43 and sudden cardiac death in DCM patients. In order to find more about the substrate of arrhythmias, DCM patients were subdivided in patients with ventricular tachycardia (VT+) or without VT (VT−) and in patients with late ventricular potentials (LP+) or without LP (LP−). Left ventricular ejection fraction was similar in VT and LP groups and the amount of fibrosis was not measured in VT groups but it was similar in LP groups. VT+ and LP+ patients showed a reduced and heterogeneous distribution of Cx43 when compared with VT− and LP−, and LP+ patients presented high susceptibility for ventricular tachycardia [67,68]. This suggests that heterogeneous reduction of Cx43, which is related with the presence of ventricular tachycardia and late ventricular potentials, may play a role in development of ventricular arrhythmias in DCM patients, possibly reflecting the patient's arrhythmic risk.

Several animal models of DCM showed similar reductions in Cx43 expression. In a canine pacing-tachycardia model of DCM, epicardial and endocardial CVs in both ventricles were decreased by more than 20% [69]. In the epicardial and endocardial LV, Cx43 expression levels were decreased by 40% with Cx43 being more expressed in epicardial than in the endocardial tissue. Contrarily, epicardial CV was further decreased when compared with endocardial CV. In both ventricles, there was lateralization and dephosphorylation of Cx43 as well as prolongation of the QRS interval although no change was detected in the action potential upstroke velocity or in fibrosis. The propensity for induced polymorphic ventricular tachycardia was increased in this model and associated with decreased wavelength [69]. In this study, the decreased epicardial CV did not seem to correlate with the increased epicardial Cx43 expression (when compared with endocardial Cx43 expression) or with reduced excitability because the action potential upstroke velocity was unchanged. The prolongation of the QRS interval can result from the remodeling of potassium currents in the failing heart like the reduction in the inward rectifier K^+ current, but also from the down-regulation in the peak of the Ca^{2+}-independent transient outward current, although Na^+ current remained unchanged [70,71]. In addition, QRS prolongation might be due to enlargement of the heart without any effect on the absolute value of CV [72]. Interestingly, another study on the same preparation has shown that Cx43 heterogeneity also leads to transmural heterogeneity of action potential duration, which may also be part of the arrhythmogenic substrate [73,74]. In the mentioned canine model it was demonstrated that the reduction of Cx43 precedes the slowing of CV, perhaps because reduction of Cx43 alone is not sufficient for conduction slowing [42,49,75]. The development of fibrosis, in conjunction with reduced Cx43 may be needed for conduction slowing [76]. The increase in dephosphorylation of Cx43 was associated with later stages of heart failure while Cx43 lateralization appears in an even later stage, when the CV is significantly reduced [75].

A mouse model of DCM induced by forced retinoic acid signaling revealed a prolongation of the QRS interval, decreased conduction velocity, increased conduction heterogeneity, regional conduction block but these mice were not susceptible to ventricular arrhythmias. A reduction of Cx43 was accompanied by Cx43 lateralization in the border zones of the affected intramural area in the LV free wall [77,78]. The heterogeneous reduction of Cx43 may play a role in the appearance of the regional conduction block. The reduction in Cx43 presumably was followed by a reduction in other intercellular junction proteins, β-catenin and N-cadherin. Besides, there was heterogeneous re-expression of the hypertrophic markers like α-skeletal actin and β-MHC and in some severely affected mice low levels of Cx40 re-expression were found [77]. Since Cx40 expression levels were low, compensation by this connexin isoform can presumably be excluded. A murine model of longstanding pressure overload subjected to transverse aortic constriction (TAC) showed an increase in LV end-diastolic and end-systolic volumes, a decrease in fractional shortening, and a rapid structural and electrical remodeling. Electrical remodeling was reflected by gradual decrease in PQ, QT and QRS prolongation and by reduced longitudinal CV in the right ventricle. Structural remodeling was reflected by heterogeneous expression of Cx43 and increased interstitial fibrosis in TAC mice while Cx43 expression levels were similar to control hearts. In this study 44% of the TAC mice were susceptible to induce polymorphic ventricular tachycardia. The only difference found in TAC mice with and without arrhythmias was a more pronounced heterogeneity of Cx43 expression in the arrhythmogenic TAC mice [79]. Thus, the arrhythmias found in this animal model of pressure overload seemed to be associated with heterogeneous expression of Cx43, which may lead to functional block and unstable reentry, resulting in polymorphic ventricular tachyarrhythmias.

Interestingly, in a pig model of DCM, expression of Cx43 was increased in the early stage of hypertrophy, but with its progression into heart failure, the levels of Cx43 decreased, cardiomyocytes myofilaments expanded and fibrosis increased [80]. Up-regulation of Cx43 in acute stages of hypertrophy in DCM but also in HCM may represent an immediate compensatory response of the heart to increased workload. A rabbit model of DCM due to surgically aortic regurgitation showed an increase in expression of Cx43 over time compared with control hearts in which expression of Cx43 remained similar up to 2.5 years [81]. This is the opposite to what was found in other animal models of DCM in which Cx43 expression decreased over time. The overall up-regulation of Cx43 in these previous studies could also result from beta-adrenergic stimulation. After 24 h of beta-adrenergic stimulation, an increase in Cx43 expression was observed in cultured neonatal rat cardiomyocytes, as well as an increase in gap junction currents [82]. However, in a different study on the same preparation, 24 h of beta-adrenergic stimulation lead to an increase in CV but had no effect on expression or distribution of Cx43, other than a slight increase in phosphorylated Cx43 [83].

In DCM, heterogeneous reduction of Cx43 seems to be closely related with the presence of ventricular tachycardia in both patient and animal models, perhaps because the concomitant development of fibrosis is prerequisite for CV slowing. Besides that, prolongation of the QRS interval is possibly related with disturbances in ion channels.

5. Ischemic cardiomyopathy

Ischemic cardiomyopathy (ICM) usually results from coronary artery disease and can be divided in an acute phase followed by a chronic

phase. The acute ischemia is associated with gap junction closure thus with reduced intercellular coupling. The chronic phase refers to healing/healed infarcts that correspond to the tissue that is recovering from the suffered ischemia and since it is a late stage, is associated with changes in the Cx43-constituent gap junction expression and/or trafficking. After acute myocardial infarction, there is the formation of a compact infarct scar surrounded by a border zone (BZ) that separates the infarct scar from normal tissue (Fig. 2) [27,29]. The BZ is composed of damaged but still viable muscle fibers, with abnormal physiological properties [84].

The presence of myocyte bridges extended across infarcted areas and coupled by gap junctions, suggests the existence of impulse propagation between areas of healthy myocardium, although in some cases those bridges were made up from a single myocyte [85]. Impulse propagation in these conditions caused transversal CV slowing due to a "zigzag" course of activation performed by impulses between healthy myocardium, although the longitudinal CV remained unchanged [86].

5.1. Acute myocardial infarction and changes in gap junction function

In a canine model of infarction, active membrane properties were largely affected in acute ischemia, followed by a partial recovery of the surviving myocytes, with the action potential duration remaining reduced [84]. One hour after ischemia, Cx43 was dephosphorylated and heterogeneously reduced in infarcted areas, and after acute ischemia small amounts of Cx43 were detected at the lateral sides of cardiomyocytes, although the signal at IDs was practically gone [87]. In an isolated perfused rabbit heart model of ischemia/reperfusion, the reduction of Cx43 over time is in accordance with that described in the canine model. Besides a redistribution of Cx43, another intercellular junction protein N-cadherin was reduced and structure integrity was altered. Despite these disturbances, epicardial CV anisotropy was unchanged [88]. In arterially blood-perfused rabbit papillary muscles there was an increased extracellular longitudinal resistance during the acute, reversible phase of myocardial ischemia, while intracellular longitudinal resistance remained unchanged, resulting in unaffected electrical coupling. During this phase, the increased extracellular resistance most likely contributed to the small slowing of CV observed. On the other hand, after 15–20 min of ischemia, increased intracellular longitudinal resistance resulted in rapid electrical uncoupling. This probably leads to CV slowing that may be an important factor for the occurrence of arrhythmias during this phase of ischemia [89]. In an isolated perfused adult rat heart model of ischemia/reperfusion a progressive dephosphorylation of Cx43 over time during ischemia was observed together with progressive electrical uncoupling and progressive reduction in total Cx43 immunofluorescent signal, while in control hearts practically all Cx43 remained phosphorylated. Although the total amount of Cx43 did not change, the decrease in total Cx43 immunofluorescent signal and increase in dephosphorylated Cx43 at IDs were probably related with the electrical uncoupling. After reperfusion, the functional recovery was associated with an increase in the phosphorylation of Cx43. These observations lead the authors to suggest that uncoupling induced by ischemia was also associated with a translocation of Cx43 from gap junctions to intracellular sites, although this was not demonstrated [90]. In neonatal rat ventricular myocyte monolayers with induced acute regional ischemia/reperfusion, a slower CV was observed after a slow recovery from Cx43 dephosphorylation during early reperfusion [91]. This slow recovery from Cx43 dephosphorylation may be a fundamental factor for the creation of a highly arrhythmogenic substrate by prolonging slow conduction after recovery of the membrane excitability. Different studies indicated the following serine positions of Cx43, Ser297/368, Ser325/328/330 or Ser365, as being phosphorylated in normal conditions and dephosphorylated during ischemia [92–94]. However, the functional consequences of (de) phosphorylation at these different sites are not known, nor the relation of dephosphorylated Cx43 with the redistribution of Cx43 from IDs to the lateral sides of myocytes.

5.2. Chronic myocardial infarction and gap junction remodeling

Areas of the BZ in human healed infarcts revealed alterations in myocyte orientation and in cell shape with more rounded or attenuated forms being present, enlargement or multiple nuclei, and disorientation of the individual myofilaments in the intact myofibrils [85]. Contrarily, areas of myocardium distant from the healed infarct appeared to be well-preserved with arrangement of fibers, IDs and an overall cellular structure resembling that of normal myocardium [85,95]. In areas of the BZ of healed infarcts a heterogeneous redistribution of Cx43 to the lateral sides of myocytes was detected in contrast with areas distant from healed infarcts, where the number of IDs remained the same as in control heart and Cx43 was confined to well-defined IDs [55,64,65,85,95]. Although these regions distant from the infarct scars (called normal zone) revealed normal Cx43 distribution, the amount of Cx43 was reduced and the cell size distribution was changed [55,64,65,95]. Up-regulation of Cx40 detected in the endocardium may represent a compensatory response to the decrease in Cx43 [64].

The BZ of infarcted canine hearts was characterized by reduced and altered kinetics of sodium current, slower CV and down-regulation of Cx43, with lateral Cx43 being more reduced than in IDs [84,88,96,97]. These observations suggest an increased axial resistivity in the transverse direction, possibly contributing this way to the development of reentrant arrhythmias [96]. Cx43 remodeling that resulted in a relative myocyte uncoupling was described together with an increase in interstitial fibrosis, distorted muscle fibers and myocyte disarray, pointing to a non-uniform anisotropic structure [84,96,98]. Concerning the electrical remodeling, another canine model of infarction presented a reduction in transverse coupling conductance [99] which is in accordance with decreased transverse CV [100], while longitudinal coupling and CV remained unchanged. Surprisingly, no reduction in Cx43 expression was detected, suggesting the presence of non-functional gap junctions, an increase in gap junction proteins dephosphorylation, or changes in other ion channels which e.g. alter the passive membrane properties [99]. The decrease in transverse conductance and CV (longitudinally oriented lines of apparent block) most probably contributed to the occurrence of reentry in this model of infarction and this is a key factor in the development of ventricular tachycardia [100]. Moreover, the abnormal redistribution and lateralization of Cx43 observed in the epicardical BZ occurred before the presence of increased fibrosis indicating an early post-infarction remodeling. This disturbance in Cx43 distribution was associated with the location of the central common pathways of the figure-of-8 reentry [101]. Cabo and coworkers [102] described some differences between the central common pathway (CCP) and outer pathway (OP) of the reentrant circuit in the canine epicardial BZ. The CV in OP myocytes was reduced with transversal CV more reduced than the longitudinal one, leading to an increase in the anisotropic ratio. In these cells the transversal gap junctional conductance decreased while the longitudinal conductance remained normal when compared to control tissue. In OP myocytes there was no Cx43 lateralization. Instead, in CCP myocytes a lateralization of Cx43 was observed. In these cells, transversal and longitudinal gap junctional conductances were similar to that of normal tissue as well as the anisotropic ratio, which reflects the equal reduction in transversal and longitudinal CVs. The decrease in longitudinal CV was bigger in CCP than in OP myocytes [102]. These changes can result from the heterogeneous remodeling of ion channels in the epicardial BZ. A previous study from the same group showed a reduction in sodium and calcium current densities in CCP and OP myocytes [103]. Thus, a combined effect of altered Cx43 and ion channel expression may explain the differences in the observed CVs. In the acute and reversible phase of myocardial ischemia in isolated porcine hearts, there was also a heterogeneous reduction in longitudinal and transversal CV and a shorter amplitude of the action potentials, which seem to be initiated by the rapid

Na^+ inward current [104]. In another rat model of myocardial ischemia, Cx43 was observed in well-defined IDs [105]. In acute ischemia Cx43, desmoplakin and cadherin expressions in the BZ of the infarct were reduced and redistributed to the lateral borders of cardiomyocytes, which further deteriorated during the chronic phase [105,106]. The IDs were remodeled, changing its form into tentacle-like structures in the BZ of the infarct, which was followed by the temporally presence of small amounts of Cx43 expression at the lateral sides of cardiomyocytes and by the increased deposition of extracellular matrix proteins like β1-integrin [105,106]. These changes may contribute to alterations of the CVs in the BZs of the infarct.

In ICM practically all the animal models presented a heterogeneous redistribution and reduction of Cx43 in the BZ of the infarcts, usually followed by slowing of CV either in the longitudinal or transverse direction, and by an ongoing increase in fibrosis. In the canine model of infarction the occurrence of reentrant arrhythmias and a decrease in the sodium current was also reported.

6. Therapies

As described above, expression of Cx43 in the heart is strongly remodeled in different forms of cardiomyopathy. Therefore, several attempts have been made to improve electrical coupling and, as a final goal, to reduce arrhythmogenesis which is frequently present in these diseases.

Some of the treatments already used in rat, rabbit, guinea pig or canine models of different cardiomyopathies are: rotigaptide, which increases gap junction intercellular communication; diltiazem, an L-type calcium channel blocker; estrogen; sotalol, a potassium channel blocker; omega-3 fatty acids, unsaturated fatty acids; atorvastatin, a member of statin class of drugs; gap26, a synthetic structural mimetic peptide deriving from the first extracellular loop of Cx43; losartan, which is an antagonist of angiotensin II type 1 receptor; apocynin, which is an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a major source of reactive oxygen species in the heart; and targeted external heavy ion beam irradiation (THIR) (Table 2).

Losartan reduced LV hypertrophy and Cx43 disorganization, as Cx43 remained mainly at IDs [60]. Inhibition of the renin–angiotensin–aldosterone system in other studies also resulted in prevention of gap junction remodeling, suppression of fibrosis, normalization of impulse conduction, and increased electrical stability [107,108]. THIR increased LV lateralization and expression of Cx43, which in normal heart lasted up to one year after a single THIR treatment and improved conductivity, decreased spatial heterogeneity of repolarization, and reduced the vulnerability for ventricular arrhythmias after myocardial infarction [109,110]. Estrogen reduced Cx43 dephosphorylation, myocyte apoptosis and infarct size, and reduced the vulnerability to ventricular arrhythmias [111–113]. Diltiazem improved LV function and reduced Cx43 dephosphorylation after reperfusion [114]. Apocynin reduced the vulnerability for ventricular arrhythmias, increased Cx43 expression and phosphorylation, decreased interstitial fibrosis and increased SERCA2a expression and activity [115,116]. The improvement in cardiac dysfunction was also characterized by shortening of QRS interval, ERP and monophasic action potential duration at 90% repolarization [115]. Sotalol prevented ischemia-induced electrical uncoupling although there was still shortening of the action potential duration and also improved electrical coupling after acute ischemia [117]. In another study sotalol increased CV and the ERP, and the propensity for induced ventricular tachycardia was markedly decreased [118]. Omega-3 fatty acids and atorvastatin increased Cx43 expression although there was a decrease in the phosphorylation of Cx43, preserved the integrity of cardiomyocytes and gap junctions, and decreased the propensity for induced ventricular fibrillation, although fibrosis was not reduced [119,120]. Gap26 protected the heart against ischemic injury by reducing the infarct size by half, either when applied before or during ischemia [121]. Rotigaptide reduced the infarct size, enhanced gap junctional conductance and suppressed reentrant ventricular tachycardia during ischemia, although no effect was observed in ERP, surface ECG parameters and blood pressure [122,123]. In epicardial BZ, rotigaptide increased Cx43 but had no effect on Cx43 phosphorylation or lateralization. However, rotigaptide in the epicardial BZ did not suppress ventricular tachycardia and did not improve CV, although the ERP was decreased [124]. Since Cx43 in epicardial BZ was not totally recovered, this could reflect the non-improvement of CV and in prevention of arrhythmias. In explanted perfused hearts from patients with end-stage heart failure, rotigaptide resulted in decreased ERP, increased longitudinal CV and normalized longitudinal conduction curves, although with destabilized transversal conduction curves [125].

Although most of the studies associate the improvement of electrical coupling as being anti-arrhythmogenic, some studies demonstrate the opposite after coronary occlusion: mice with 50% reduction of Cx43 presented an infarct size smaller than in normal mice [126]; mice with a deletion of the carboxyl terminal domain of Cx43 showed an increase in the infarct size [127]; and mice expressing Cx32, which is a connexin isoform pH- and voltage-independent, presented an increase in infarct size compared with control mice [128,129]. The effect on arrhythmogeneity was found to be beneficial [129] or absent [128]. Therefore, improving intercellular coupling during acute ischemia can have anti-arrhythmic effects, but will also lead to increased infarct size after coronary occlusion.

These findings suggest that strategies that suppress Cx43 remodeling can be potential new anti-arrhythmic targets, especially in the context of heart failure associated arrhythmias. The opportunities for treatment of ischemia related arrhythmias are more limited, because reduction of arrhythmogeneity is achieved at the cost of increased infarct size.

7. Conclusions

Abnormal Cx43 expression in the heart has been reported in several forms of cardiomyopathies as hypertrophic, dilated and ischemic cardiomyopathy. Generally, Cx43 is down-regulated and heterogeneously redistributed throughout the heart, and in some cases it is lateralized. This abnormal Cx43 expression is often followed by a reduction in the CV, which then seems to be accompanied by an increase in fibrosis. All these disturbances may lead somehow to the development of arrhythmias (Fig. 3). In addition, ventricular tachycardia seems to be associated with the heterogeneous reduction of Cx43. One of the explanations for conduction slowing is the Cx43 redistribution and the decrease in the phosphorylation of Cx43, but other factors can also be involved like altered repolarization phase and a reduction in the sodium current. An interesting factor in the ischemic heart is the up-regulation of Cx43 in fibroblasts [130], that can also play a role in the disturbance of the CVs. Prolongation of the QRS interval can possibly be related with disturbances in ion channels and prolongation of the action potential duration can possibly be related with the decrease in the intercellular coupling conductance [131]. In addition to the general down-regulation of Cx43, in some cases Cx43 is up-regulated in early, compensated stage of hypertrophy but followed by a down-regulation, which could reflect a compensatory mechanism to the workload.

Several approaches that successively improved Cx43 expression levels or Cx43 conductance and reduced the vulnerability for ventricular arrhythmias open the opportunity for potentially new anti-arrhythmic therapies for heart failure.

In conclusion, the functional consequences of reduced and heterogeneous Cx43 expression in the heart are slow and dispersed impulse conduction, which may increase the propensity to generate arrhythmias, especially when combined with increased fibrosis. Treatments aimed to improve the Cx43 expression levels show new potentially anti-arrhythmic therapies during heart failure, but those in the context of

Table 2
Therapy treatments to reverse the abnormal Cx43 expression in heart remodeling.

Therapy	Tissue origin	Cx43				Fibrosis	CV	Arrhythmias	Comments	References
		Expression	Phosphorylation	Distribution						
				Heterogeneous	Lateralized					
Losartan	Rat			↓	↓				↓ LV hypertrophy	[60]
THIR	Rabbit	↑			↑		↑	↓	↓ Spatial heterogeneity of repolarization	[109]
Estrogen	Rat		↑					↓	↓ Myocyte apoptosis	[111]
			↑						↓ Infarct size, ↓ free radicals	[113]
		↑			↓			↓		[112]
Diltiazem	Rat		↑						↑ LV function	[114]
Apocynin	Rabbit	↑	↑			↓		↓	↑ SERCA2a expression and activity, ↓ QRS interval, ↓ ERP, ↓ MAP duration at 90% repolarization	[115,116]
Sotalol	Guinea Pig								Recovery of electrical coupling, ↓ APD	[117]
	Rabbit						↑	↓	↑ ERP	[118]
Omega-3 fatty acids	Rat	↑				=		↓	= Hypertrophy	[119]
			↓		↓			↓	Preservation of cardiomyocytes and gap junctions integrity	[120]
Atorvastatin	Rat		↓		↓			↓	Preservation of cardiomyocytes and gap junctions integrity	[120]
Gap26	Rat								↓ Infarct size	[121]
Rotigaptide	Canine							↓	↑ Conductance = ERP, surface ECG, mean arterial pressure or infarct size	[122]
		↑ (gap junctions in general)						↓	↓ Infarct size = Surface ECG, blood pressure	[123]
		↑ (EBZ)	= (EBZ)		= (EBZ)		= (EBZ)	= (EBZ)	↓ ERP	[135]
	Human (*ex-vivo*)						↑ CV_L		↓ ERP Destabilized transversal conduction curves	[136]

Abbreviations: THIR, targeted external heavy ion beam irradiation; ↑, increased; ↓, decreased; =, no effect; LV, left ventricle; CV_L, longitudinal conduction velocity; EBZ, epicardial border zone; ERP, effective refractory period; MAP, monophasic action potential; APD, action potential duration; ECG, electrocardiography.

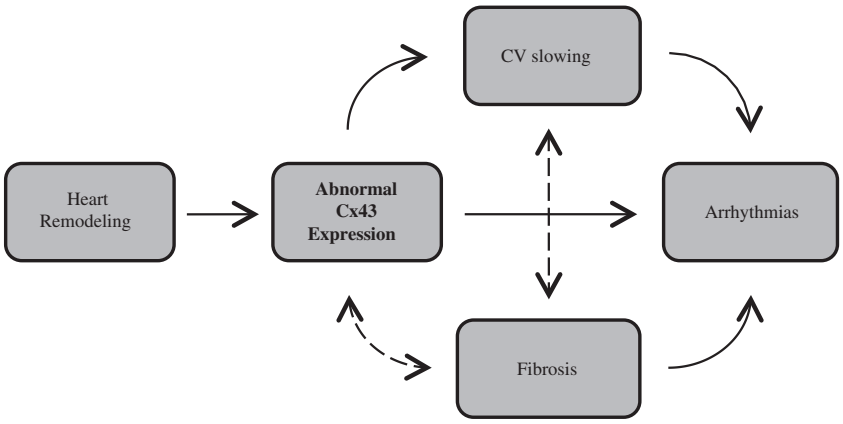

Fig. 3. Functional consequences of abnormal Cx43 expression after heart remodeling.

acute ischemia can be anti-arrhythmogenic at the cost of larger infarct sizes.

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