Biochimica et Biophysica Acta 1832 (2013) 2432–2441

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Electrophysiological changes in heart failure and their implications for arrhythmogenesis ☆,☆☆,★

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ARTICLE INFO

Article history:
Received 31 December 2012
Accepted 1 April 2013
Available online 8 April 2013

Keywords:
Heart failure
Arrhythmia mechanism
Intercellular coupling
Diet
Stretch
Pulmonary hypertension

ABSTRACT

Heart failure is the final common pathway of various cardiac pathologies and is associated with sudden cardiac death, mostly caused by ventricular arrhythmias. In this paper we briefly review the electrophysiological remodeling and the alterations in intracellular calcium handling, and the resulting arrhythmogenic mechanisms associated with heart failure. Intercellular uncoupling and fibrosis are identified as a major arrhythmogenic factors. Diet and ventricular wall stretch are discussed as modulating factors. Finally, emphasis is placed on the hitherto poorly studied aspects of right ventricular failure. This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

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1. Introduction

Heart failure is associated with life threatening ventricular arrhythmias. Although about 50% of deaths in patients with heart failure is caused by pump failure, the remainder is associated with cardiac arrhythmias [1]. The mechanisms of these arrhythmias differ and depend on the underlying electrophysiological changes caused not only by heart failure itself but also by the processes that have led to heart failure in the first place.

The definition of heart failure is subject to debate, but it is generally considered a syndrome in which the pumping action of the heart falls short to provide a sufficient amount of blood and oxygen to the organs (including the heart itself) [2,3]. Heart failure is the final common pathway of a multitude of cardiac pathologies [2], the most common of which is myocardial infarction. In the course of time after the onset of myocardial infarction, the loss of myocardium and the associated loss of contractile function are compensated by cardiac hypertrophy. Eventually, this may result in failure. Other cardiovascular diseases also eventually result in heart failure: (corrected) congenital cardiac abnormalities, valve disease, hypertension, dilated cardiomyopathy, hypertrophic cardiomyopathy, Chagas' disease, arrhythmogenic right ventricular cardiomyopathy, tachycardia dependent cardiomyopathy and so forth. The primary electrophysiological changes and the mechanism of arrhythmogenesis associated with heart failure therefore depend on the cause of heart failure. This is equally true for the mechanism of the trigger of the arrhythmia as for the electrophysiological substrate. This is one of the explanations why cardiac arrhythmias in heart failure are so difficult to treat and why the choice of the therapeutic approach is not straightforward [4,5].

The electrophysiological changes during heart failure are, therefore, multiple, and dependent on the underlying disease. They involve ion channel remodeling, alterations in calcium handling, remodeling of the extracellular matrix, the presence of scars, activation of the sympathetic nervous system and the renin–angiotensin–aldosterone-system, and dilatation and stretch. In addition, insufficient blood supply associated with heart failure may also affect the heart and may lead to acute myocardial ischemia, with its own arrhythmogenic mechanisms [6]. Thus, heart failure is not characterized by a single set of electrophysiological changes.

As a consequence of the complexity of the electrophysiological changes that may occur during heart failure, the scientific literature on the subject is not unequivocal and highly dependent on the model used to study these changes. Electrophysiological changes occurring in

☆ Disclosures: none.
☆☆ This study is supported by: The Netherlands Heart Foundation (grant NHS2007B018).
★ This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

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http://dx.doi.org/10.1016/j.bbadis.2013.04.002

a pressure and volume overload model of heart failure in a rabbit heart [7,8] do not necessarily mirror those observed in a dog model of infarction and pacing-induced heart failure [9], or those in a mouse model with a junctophilin mutation [10]. In addition, patients with heart failure receive pharmacological or non-pharmacological therapy to increase hemodynamic function, to treat dyspnea, to synchronize contraction, or to suppress arrhythmias. These therapies are almost never applied in animal models and this further limits translation of the experimental data to the clinical situation.

This review focuses on some of the common denominators of heart failure induced changes that are relevant for arrhythmogenesis, and which include ion channel remodeling, cellular uncoupling, altered calcium homeostasis, and extracellular matrix changes. A short section will deal with the influence of myocardial stretch on electrophysiology. Because heart failure can be considered as a deficit of energy delivery, its development and electrophysiological consequences heavily depend on the use of metabolic substrates. Some words will therefore be dedicated to dietary modulation of heart failure in relation to electrophysiological changes. Finally, a section will be dedicated to the idiosyncrasies of right ventricular failure, an increasingly common consequence of corrected congenital cardiac disease [11].

2. Ion channel remodeling

Action potential prolongation is a common feature in almost all experimental models of heart failure [12,13] as well as in patients with heart failure [8,14], and is an expression of reduced repolarization reserve [15]. Repolarization reserve is defined as the ability to effect repolarization even if one of the repolarizing currents is reduced (by drug action, genetic mutation, or disease) or if more depolarizing current is present than normal. Indeed, T-wave changes as well as QTc prolongation are seen clinically. The T-wave changes are often explained as a consequence of myocardial strain. Direct evidence for this is lacking, although tissue strain does affect ventricular repolarization characteristics [16].

Another expression of reduced repolarization reserve is T-wave alternans. It has been suggested that T-wave alternans is a predictor of sudden cardiac death [17]. Indeed, during acute myocardial ischemia the onset of ventricular fibrillation is preceded by overt T-wave alternans [18]. Recently, techniques have been developed to quantify subtle T-wave changes on a beat to beat basis clinically. Micro-T-wave alternans analysis (MTWA) has been tested in a large group of patients with heart failure by Jackson et al. to study the applicability of MTWA [19]. The authors concluded that in most cases the test was indeterminate, if the test could be applied, and that the role of MTWA for risk stratification is meager.

The prolongation of the ventricular action potential in heart failure (for review see [20,21]) is depicted schematically in Fig. 1 (reproduced from Michael et al. [20]) in association with the changes in Ca^{2+}-handling. It has been proposed that the AP-prolonging effects compensate for the loss of contraction by increasing the amplitude and/or the duration of the Ca^{2+}-transient. AP-prolongation results from a reduction of the repolarizing currents I_{to} and I_{Ks}, alone or in combination with an increase in a late inward current carried by Na^{+}. The latter current is almost non-existent in normal myocardium. Terminal repolarization is postponed by a reduction of I_{K1} in some models of severe heart failure. The latter also results in a decreased stability of the resting membrane, by which the myocardium becomes more susceptible to spontaneous depolarizations (see following section).

The presence of sodium channel remodeling likely depends on the model of heart failure used, although an increase in late sodium current is a consistent finding. In a model of myocardial infarction in dogs border zone myocytes demonstrate sodium channel remodeling leading to a reduced peak sodium current [22]. This may contribute to slowing of propagation.

2.1. QT-prolongations and arrhythmogensis

A prolonged QT-interval in itself predisposes for the genesis of early after depolarizations (EADs), which in turn may induce Torsade des Pointes ventricular tachycardias or ventricular fibrillation. In the latter case the EADs act as a trigger for the arrhythmia with a reentrant mechanism. In a mapping study of a rabbit model of pressure and volume overload a combined focal and reentrant mechanism of arrhythmias has been described [23], compatible with this concept. Myocardium excised from human hearts with heart failure also has demonstrated EADs but not sustained arrhythmias. The mass of tissue was apparently too small to support a reentrant arrhythmia [8].

Increased QT-dispersion in patients with heart failure [24] has been associated with increased dispersion in repolarization, which favors the initiation of a reentrant arrhythmia [25–27] especially if combined with a critical degree of conduction slowing in the area with the prolonged repolarization [28]. Cellular uncoupling may unmask intrinsic differences in repolarization [29] and thereby increase repolarization heterogeneity. At the same time it may contribute to conduction slowing and facilitate reentrant arrhythmias.

3. Intercellular uncoupling

3.1. Connexin43 expression and conduction

A decreased expression of the major gap junctional protein connexin43 (Cx43) is also a general feature of heart failure. Cx43 expression is reduced by up to 50% and part of the protein is dephosphorylated [29,30]. This protein is responsible for cell–cell communication both electrically and physically (it permits the exchange of small molecules between cells). Whereas in the healthy myocyte connexins are located preferentially at short sides of the myocyte, the connexins redistribute during heart failure and are also found along the long sides of the cell [31].

Cellular coupling is important for conduction of the cardiac impulse, and a high degree of redundancy exists in the amount of protein. Conduction changes occur only at large reductions of Cx43 [32–34] that are probably not reached during heart failure. However, the combination of moderate intercellular uncoupling and a reduction of sodium current could lead to conduction slowing [35]. However, in a rabbit model of moderate to severe heart failure that is associated with sudden cardiac death and arrhythmias a reduction of Cx43 expression was associated with a paradoxically increased epicardial conduction velocity [36]. In that same model, QRS duration was increased, because the increased conduction velocity could not fully compensate for the increase in myocellular dimensions resulting from hypertrophy [36].

Pharmacological tools have been developed to maintain the phosphorylation status of Cx43 and thereby increasing cellular coupling. Indeed, rotigaptide administration leads to increased (atrial) conduction velocity and prevented ischemia induced conduction slowing [37]. However, rotigaptide may also cause increased anisotropy of conduction, and may eventually lead to transverse activation block and arrhythmias [38].

Because Cx43 is part of a macromolecular complex in which the sodium channel is also involved [32,39], it is to be expected that alterations in one part of this macromolecular complex has consequences for other parts. Therefore, sodium channel dysfunction likely accompanies Cx43 downregulation during heart failure, even in the absence of a direct HF-induced effect on the sodium channel.

3.2. Connexin43 expression and repolarization

There is indirect evidence that intercellular uncoupling may also impact on QT-changes in heart failure. In the same animal model of heart failure as described above [36] QT prolongation was observed

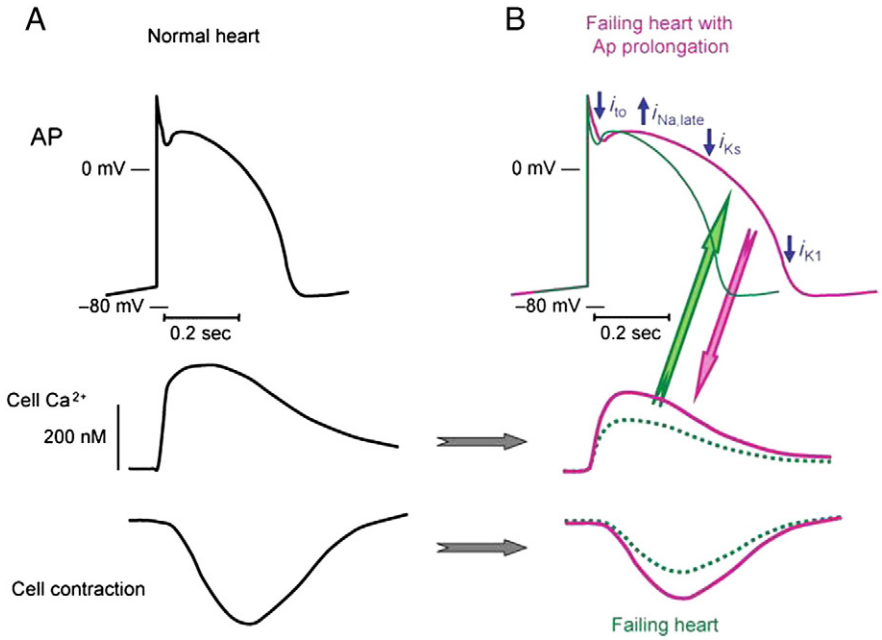


Fig. 1. A schematic diagram showing the changes in Ca^{2+}-handling and contractility and the potential compensatory function of ion-channel remodeling that causes action potential (AP) duration (APD) prolongation in congestive heart failure. A. A normal cardiac AP, along with associated changes in free intracellular Ca^{2+}-activity (upward deflection indicates increased Ca^{2+}-concentration) and systolic cell contraction (downward deflection indicates cell length decrease). B. Ca^{2+}-concentrations and cell contraction in the failing heart are shown by the green dotted lines. Decreased systolic Ca^{2+}- release impairs cellular contractility and causes APD-prolonging ion current remodeling (changes are indicated by the arrows indicating increases or decreases in specific currents).
Reproduced with permission from ref [20]

in vivo at a physiological heart rate [40] (Fig. 2A). Action potential prolongation was not observed in isolated ventricular myocytes obtained from the same hearts at a (physiological) stimulation rate of 4 Hz (Fig. 2), although it was observed at physiologically irrelevant low heart rates,. In transmural tissue samples taken from the LV free wall of HF rabbit hearts, connexin43 expression was reduced by ≈50% [36]. Yet, the transmural conduction velocity was unchanged and amounted to 24–25 cm/s, [36,29] suggesting that the negative effect of intercellular uncoupling on transmural conduction velocity is compensated by the increase in cell dimensions, which facilitates conduction [36]. The net effect of the unchanged conduction velocity and the increased cell dimensions was an increased transmural activation time. This was corroborated in computer simulations of a transmural strand of 200 myocytes (first 100 with endocardial characteristics (long action potential, I_{to} absent), next 100 with epicardial characteristics (short action potential, I_{to} large) [41]), as diagrammed in Fig. 2D (left). Under control conditions, the model, fed with the mean control cell dimensions of Fig. 2B, required a gap junctional conductance (g_j) of 8 μS to assure a conduction velocity of 25 cm/s. The subepicardial cells repolarized to 90% ≈2 ms before the subendocardial cells (Fig. 2D, middle). If g_j was halved to 4 μS and the mean HF cell dimensions (Fig. 2B) were used while the intrinsic action potential characteristics were maintained, the conduction velocity remained 24–25 cm/s, but the transmural activation time was increased by ≈10 ms. As a result, the time from first activation to last repolarization (90%) had increased about 7 ms in the HF simulation compared to the control condition. In addition, the subepicardial cells repolarized later than the subendocardial cells (Fig. 2D, right).

These simulations show that the decreased coupling observed during HF causes 1) an increase in transmural activation times and 2) unmasking of the intrinsic heterogeneity in repolarization. The combination of these effects results in a prolongation of the time between earliest activation and last repolarization and may explain both the increase in QT-interval in the paradoxical presence of unchanged action potential duration, and the inversion of the T-wave as observed experimentally. Although the effects from this simulation of a strand of myocardium appear small, they may be more pronounced in an entire heart.

4. Altered calcium homeostasis

Heart failure is associated with altered calcium handling. Whereas a healthy heart demonstrates a positive force–frequency relation, it is reversed in failing hearts. This is reflected in the reversed frequency dependence of the amplitude of the Ca^{2+}-transients in heart failure [42]. In addition, the diastolic Ca^{2+}-concentration is elevated [42]. The sarcoplasmic (SR) calcium content is decreased in a stimulation rate-dependent manner, leading to a smaller amplitude of the Ca^{2+}-transient especially at higher heart rates. Also, the SR Ca^{2+}-ATPase is down regulated, leading to a slower reuptake of Ca^{2+} into the SR and a slowing of relaxation [43]. These conditions allow the occurrence of spontaneous Ca^{2+}-releases from the SR ('Ca^{2+}-sparks') [44].

During heart failure the sarcolemmal Na^+/Ca^{2+} exchanger (NCX) is upregulated and allows the removal of Ca^{2+} out of the cell [43]. Because the NCX is electrogenic and moves three sodium ions against one calcium ion, it may generate an inward current under conditions of intracellular calcium overload. Spontaneous calcium release events, therefore, are accompanied by transient depolarizations of the resting membrane, showing as delayed after depolarizations (DADs). These DADs may in turn trigger full action potentials and cause arrhythmias based on triggered activity (see Fig. 3) [21,42]. Prolongation of the action potential (see above) may contribute to this arrhythmogenic mechanisms when it is accompanied by a shortening of the diastolic interval which reduces the time available to remove excess cytoplasmic Ca^{2+}.

Altered intracellular calcium homeostasis in heart failure does not only have consequences for the transmembrane current, SR-loading and arrhythmogenesis, but also for various signaling pathways in which Ca^{2+} is centrally involved, amongst others in hypertrophic signaling and cell death [45]. This topic impacts on the structural changes occurring in heart failure that may influence arrhythmogenesis but is

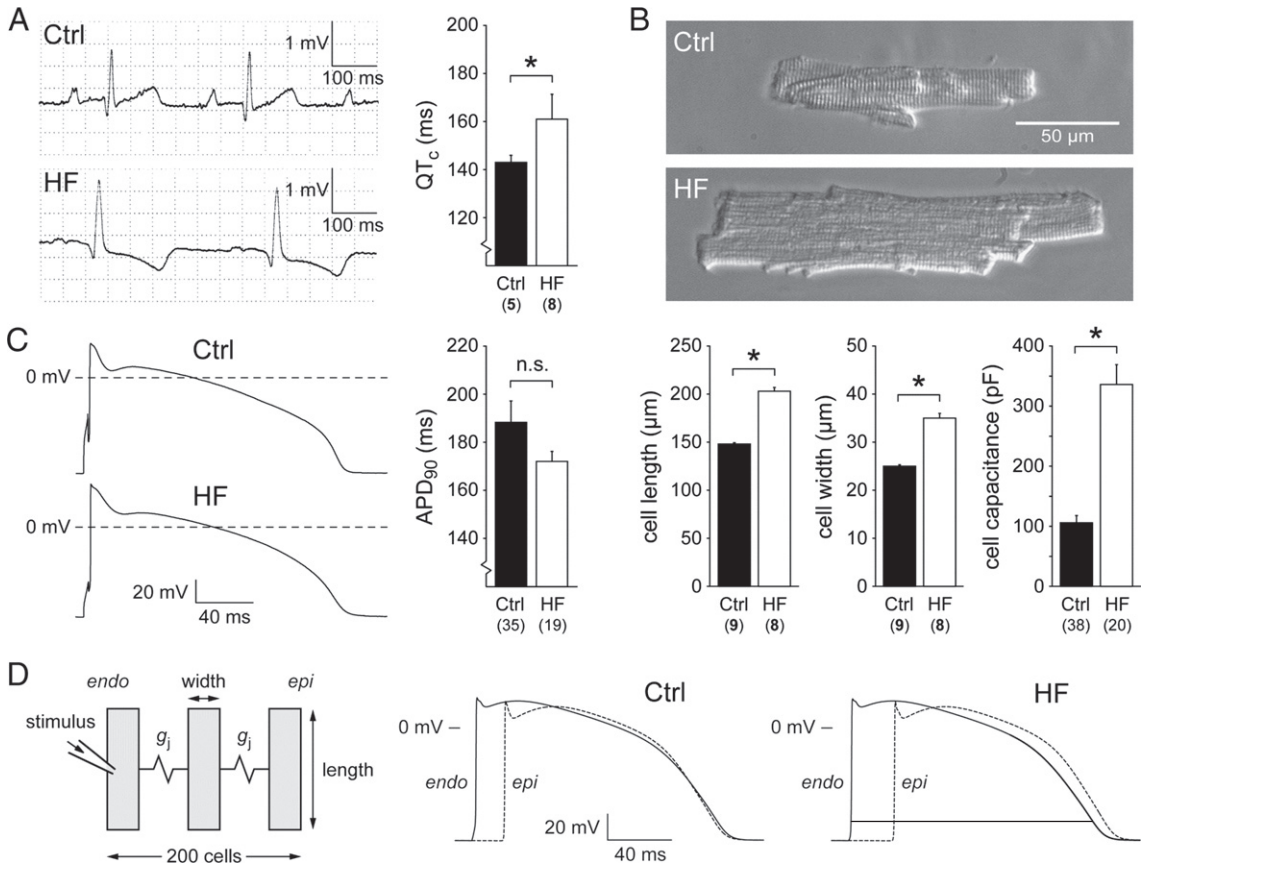


Fig. 2. QT prolongation and intercellular uncoupling. A. Typical ECG traces (lead I) from a control rabbit (Ctrl) and from a rabbit with heart failure (HF) and QTc intervals (n: number of animals, data from Den Ruijter et al. [40]). Bars show mean ± SEM. Asterisks indicate significant difference ($p < 0.05$, HF vs. control). Note the inversion of the T-wave in HF. B. Photographs of an isolated ventricular myocyte from a control rabbit (top) and from a rabbit with HF (bottom), cell length and (n: number of hearts, 50 myocytes/heart, data from Verkerk et al. [101]), and cell capacitance of 38 control and 20 HF myocytes (data from Verkerk et al. [101]). C. Action potentials recorded from ventricular myocytes isolated from a control rabbit (top) and from a rabbit with HF (bottom) and associated action potential duration at 90% repolarization (APD_{90}) (n: number of myocytes). Action potentials elicited at 4 Hz and recorded with the perforated patch clamp technique. Data from Den Ruijter et al. [40]. Bars show mean ± SEM. Asterisks indicate significant difference ($p < 0.05$, HF vs. control). D. Effect of intercellular uncoupling as observed in HF on endocardial and epicardial action potentials as observed in the 10th cell from the endocardial side (solid line labelled 'endo') and in the 10th cell from the epicardial side (dashed line labelled 'epi') in a simulated strand of 200 transversally arranged myocytes coupled by a gap junctional conductance g_j. Action potentials elicited at 4 Hz by a stimulus applied to the first cell at the endocardial side. The horizontal line in panel D represents the time from earliest activation to last repolarization under control conditions.

outside the scope of this review (see also the contribution of Wehrens et al. in this issue).

5. Extracellular matrix

During heart failure the myocardium undergoes structural changes that lead to fibrosis [46,47]. Fig. 4A shows picrosirius red staining of left ventricular apical biopsies obtained during cardiac transplantation (lower two panels) in comparison with a control biopsy from rejected donor hearts (considered as a normal control biopsy) [48]. Panel B shows the quantification of fibrosis indicating an increased amount of fibrosis in the hearts from patients with end-stage heart failure ($n = 15$) compared to control ($n = 10$). It cannot be excluded that a difference in age may have contributed to the difference in fibrosis, but the figure suggests that HF is associated with the fibrosis. The data could be reproduced in a mouse model of heart failure (after transaortic constriction) in which the ages of the mice were similar [48].

The altered extracellular matrix contributes to a decrease in diastolic function of the heart. For cardiac electrophysiology it is important that the collagenous septa separating the myocardial fibers may impede propagation of the cardiac impulse, especially transverse to fiber direction, by disruption of the (lateral) intercellular coupling. The resulting increased anisotropy may not only facilitate the genesis of a focal arrhythmia [49], but may also contribute to current-to-load mismatch conditions and conduction block, especially when the sodium and calcium currents are reduced [50]. The arrhythmogenic potential of subtle structural alteration in combination with sodium channel dysfunction is demonstrated in patients with Brugada syndrome who are at increased risk for sudden cardiac death and many of whom have structural changes in the right ventricular outflow tract in combination with a sodium channel mutation [51].

Fibrosis is associated with electrogram fractionation. Spach et al. have shown how electrogram morphology depends on anisotropy [52]. In the setting of myocardial infarction De Bakker et al. have shown how the various components of a fractionated local electrogram correspond to propagation in an individual muscle fiber of a human left ventricular papillary muscle obtained during cardiac transplantation [53]. Activation in the fibrotic muscle propagated in a zig-zag fashion along the electrically isolated fibers, and led to a significant activation delay, although conduction velocity in the individual fibers was not slowed [53]. In these cases the activation delay was caused by the large increment in the length of the activation path, and not by a depression of sodium channel function. Activation delay over a small distance facilitates reentrant activation, particularly in combination with a shortened refractory period [25].

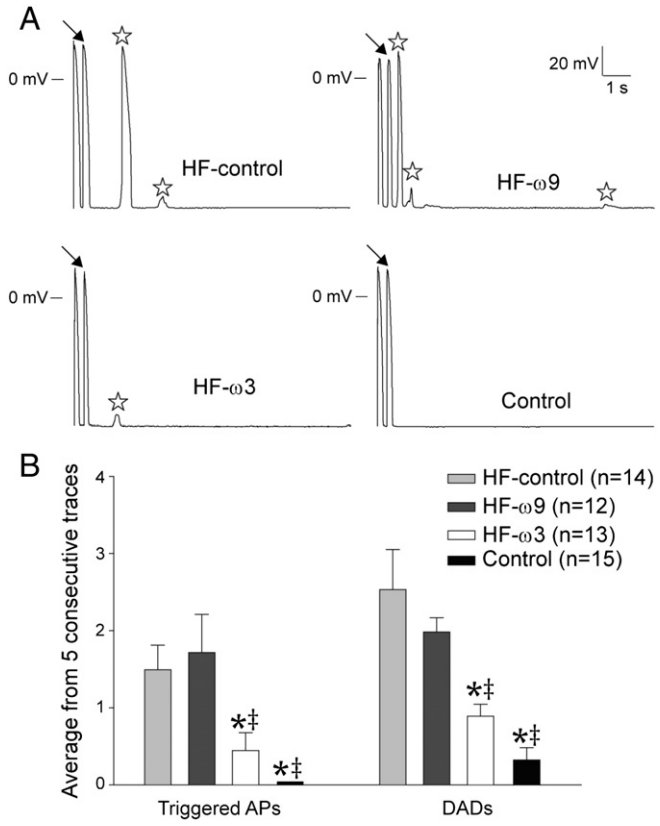


Fig. 3. Fish oil prevents triggered activity. A. Representative examples of the tracing periods. Arrows indicate last paced AP. Note that the pacing period is followed by a delayed after depolarization (DAD) and triggered activity in hearts from animals with heart failure (HF) (HF-control) but not in healthy hearts (Control). B. Data summary of the number of triggered APs and delayed after depolarizations (DADs). Bars show mean ± SEM. *p < 0.05 vs HF-control and ‡p < 0.05 vs. HF-ω9 (one-way ANOVA). Reproduced with permission from ref [40].

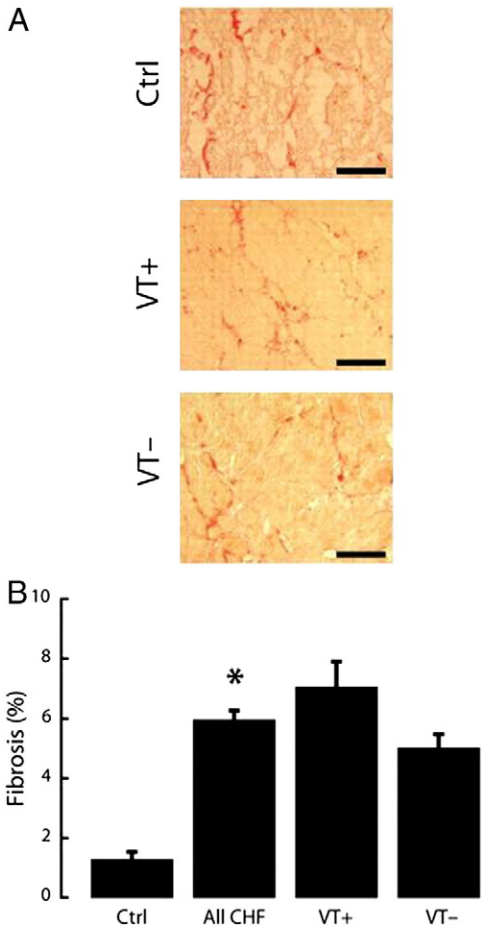


Fig. 4. Increased fibrosis in hearts from patients with end-stage heart failure, with and without ventricular arrhythmias (VT+, VT−; n = 7 and n = 8, respectively), who underwent cardiac transplantation. Ctrl denotes hearts from heart donors (n = 7). CHF: congestive heart failure. Bars show mean ± SEM. * statistically significant difference vs. Ctrl.
Reproduced with permission from [48].

5.1. Implications for arrhythmogenesis

Fine structural changes similar to those that occur in heart failure may thus contribute significantly to arrhythmogenesis. The dependence of fractionation during premature stimulation was applied clinically to identify patients at risk of sudden death [54]. Kawara et al. have described the conditions for the occurrence of fractionated unipolar electrograms in explanted hearts from patients with end-stage heart failure [55]. It appeared that activation delay increased with progressively shorter coupling intervals, especially when the direction of propagation was perpendicular to fiber direction, and when fibrosis was organized into long fibrotic strands. Diffuse fibrosis was not associated with the activation delay [55].

6. Arrhythmogenic mechanisms

The mechanism of arrhythmogenesis depends on the myocardial structure in combination with the degree of electrophysiological remodeling and Ca^{2+}-handling alterations. Whereas the latter two define the mechanism of initiation ('the trigger') of the arrhythmia, the structure defines the mechanisms of the continuation of the arrhythmia in combination with spatial heterogeneities in the degree of electrophysiological remodeling. These considerations have consequences for the choice of therapy.

Fig. 5 summarizes the complex manner in which structural and functional changes that occur during heart failure interact to lead to arrhythmias. Cellular ionic remodeling and altered Ca^{2+}-handling (left upper panel) cause the generation of EADs and DADs, that may lead to a triggered premature beat. If this premature beat is coincident with a suitable substrate (repolarization heterogeneity, uncoupling and/or fibrosis, left lower panel) reentry may ensue. Dependent on the extent of the scar or the degree of organization of fibrosis a large or small reentrant circuit may be set up (right lower panel). In the case of a large reentrant circuit (with the circuit length being larger than the wavelength, defined as the mathematical product of local conduction velocity and local refractory period) an excitable gap, a period between repolarization and the subsequent activation, will exist during which the cell membrane has regained its resting membrane potential. With a finer structure of fibrosis (or uncoupling) reentry of a different nature will be more likely to develop, with a smaller or even absent excitable gap. Although the relation between the type of reentry and tissue architecture has not been accurately described, it is likely that in hearts with diffuse fibrosis one or more rotors may maintain the arrhythmia whereby the tissue discontinuities may function as (temporary) anchoring points for the mother rotor [56]. If triggered activity persists (right upper panel) it may in itself be the mechanism for focal perpetuation of the arrhythmia, unless it converts into reentry.

Therapeutic options depend on this conglomerate of factors. For example, catheter ablation therapy may allow modulation of the substrate if a single focus exists, or if a reentrant activation circuit follows a fixed pathway. An organized myocardial scar evidently may form the basis of a macro-reentrant circuit, whereas fine structural abnormalities tend to be associated with a wandering rotor that has multiple anchoring points at the abundant tissue heterogeneities [57].

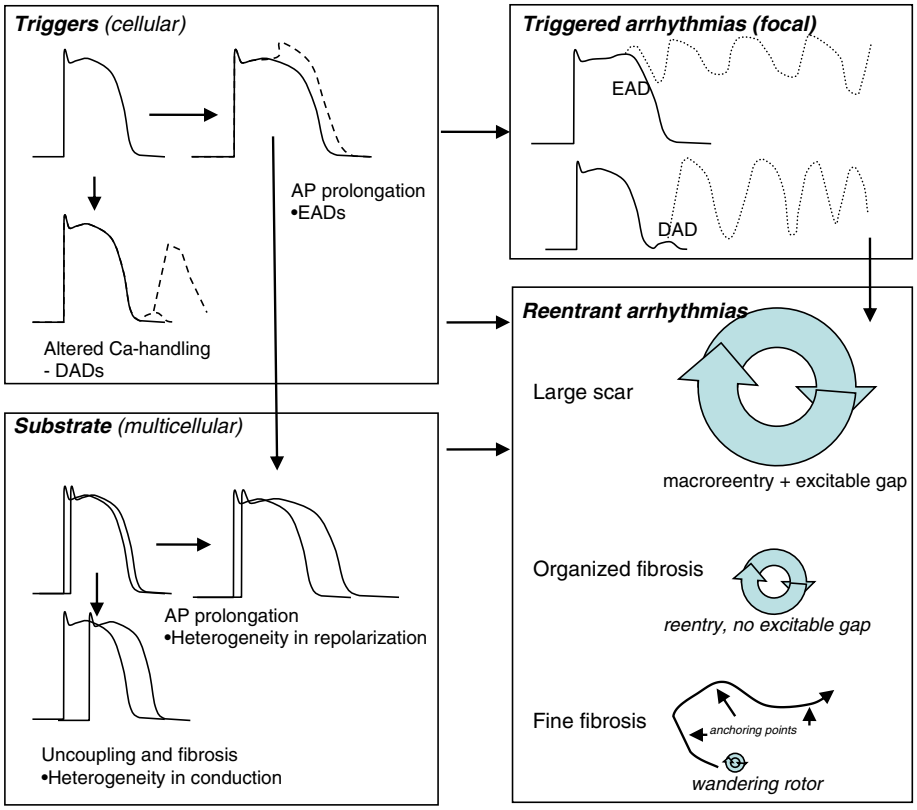


Fig. 5. Diagram of the interaction between the cellular and multicellular arrhythmogenic mechanisms leading to arrhythmogenesis in heart failure.

Catheter ablation is less likely to result in arrhythmia prevention if the substrate is based on a wandering rotor in a substrate of fine fibrosis. The challenge for clinical cardiology is to identify the type of structural remodeling in each patient with heart failure and thereby to identify the best therapeutic options.

Apart from the key requirements for arrhythmogenesis, many modulatory factors play a role [58]. Examples of the modulation of the triggering and substrate are the influence of the autonomic nervous system, pharmacological treatment, mechanical action of the heart and diet. We will briefly discuss the latter two of these factors. Some of the other modulating factors are discussed elsewhere in this issue (references to be provided by editor).

7. Modulation

7.1. Wall motion

Heart failure is a common consequence of myocardial infarction and often involves abnormal wall motion in some parts of the heart. Abnormal wall motion is a strong predictor of sudden cardiac death [59]. Myocardial stretch and dilatation are associated with opening of stretch sensitive ion channels and with arrhythmias [16,60,61]. Kamkin et al. have demonstrated that myocytes from human, guinea pig and rat hearts show membrane depolarization upon stretching, action potential prolongation and spontaneous activity. The membrane current underlying these changes was inhibited by Gadolinium, and the changes were more outspoken in hypertrophied myocytes [62].

In a recent paper, Opthof et al. have reported on the role of wall motion abnormalities on dispersion in repolarization in patients (with and without previous myocardial infarction) undergoing cardiac surgery [63]. Local unipolar electrograms were obtained from up to 72 left ventricular epicardial sites and activation recovery intervals (ARIs) were measured as an index of action potential duration. Wall motion was measured simultaneously with esophageal echocardiography in 9 left ventricular regions of the heart. It appeared that in the presence of wall motion abnormalities the difference of ARIs between the 9 regions of the heart was larger than in patients without wall motion abnormalities, independent of the presence of myocardial infarction. Importantly, the overall increased dispersion in ARIs was caused by increased dispersion of ARIs within the normally moving myocardium. The dispersion in ARIs also was associated with dispersion in repolarization time, which forms one of the required substrates for the initiation of reentry [25,27]. In summary, these data suggest that wall motion abnormalities may directly create or increase the substrate for reentrant arrhythmias [63].

7.2. Diet

The GISSI study has demonstrated that a diet rich in fish oil (resembling the Mediterranean diet) reduces the risk of sudden cardiac death in a large population of patients with a prior myocardial infarction [64]. There is ample experimental evidence for the effects of fish oil fatty acids on myocardial electrophysiology [65]. Acute administration of fish oil prevented ventricular fibrillation in dogs [66]. Dietary supplementation with fish oil fatty acids causes a reduction of the action potential duration in pigs [67] and may thus antagonize the heart failure induced prolongation of the action potential duration and its arrhythmogenic consequences (see also Fig. 3) [68]. In addition to these direct electrophysiological effects of fish oil fatty acids, a diet rich in unsaturated fatty acids may force energy metabolism of the cardiac myocyte towards maintenance of beta-oxidation and slow development of heart failure [40]. The latter mechanism establishes an indirect effect that results in less arrhythmogenesis.

Action potential shortening is anti-arrhythmic if the primary arrhythmogenic mechanism is based on action potential prolongation, but it may be pro-arrhythmic when the primary mechanism is based on reentry, because in the latter case it may reduce wave length [65]. Indeed, pro-arrhythmic effects of dietary fish oil fatty

acids have been described [69,70]. This paradox may explain why studies involving a net effect of dietary fish oil supplementation in large patient groups has not been demonstrated [71].

8. Right ventricular failure

Right ventricular (RV) failure develops as a consequence of a variety of pathological condition such as RV infarction, pulmonary hypertension, genetic disorders (e.g. arrhythmogenic right ventricular cardiomyopathy (ARVC)), or in the context of corrected congenital cardiac disease such as surgical repair of Tetralogy of Fallot (TOF). It can also occur secondary to left-sided heart failure. Lou et al. describe pro-arrhythmic electrophysiological remodeling in *ex vivo* human RVs regardless of the anatomical origin (left or right side) of heart failure [72] suggesting that the RV might be involved in arrhythmia generation and maintenance independent of the ventricular origin of heart failure.

Although RV arrhythmias and sudden cardiac death are common features of these pathological conditions [73], the electrophysiological remodeling and the mechanisms involved in arrhythmia generation in the failing RV remain relatively understudied compared to the left ventricle (LV).

APD prolongation, a hallmark of LV heart failure, has also been consistently observed in the failing RV myocardium [74–76]. On the ECG of patients with RV dysfunction, this prolongation is typically reflected by an increased duration of the QT-interval [77–79] although a concomitant electrophysiological remodeling of the LV is also likely to contribute to this effect [80]. In the pressure-overloaded RV of the rat, the APD prolongation appeared to be related to a decrease in the expression of the main potassium channels [76]. APD dispersion is also increased in the failing RV when measured in isolated ventricular myocytes [81] and at the RV epicardial surface of perfused isolated hearts where the right ventricular outflow tract shows the longest APD [82].

Conduction abnormalities are commonly found in right heart failure and are linked not only to changes in the expression, localization and phosphorylation of gap junctions [83,84], altered sodium current properties [85], and fibrosis [86] but also to scars in ARVC and TOF patients after corrective surgery [87,88]. Indeed, an increased duration of the QRS interval of patients with repaired TOF or ARVC reflects activation delays [89,90] and loss of synchronicity [91,92]. The presence of QRS fragmentation, which is related to scar size, is a good predictor of arrhythmias in these pathological conditions [93,94]). Electrical maladaptation to a change rate observed in the failing RV in the form of steep APD and conduction velocity (CV) restitution curves, could lead to alternans, an established predictor of sudden cardiac death [17,82,95].

As in LV failure, altered calcium homeostasis is also likely to play an important role in RV dysfunction and arrhythmogenesis. Sarcoplasmic reticulum (SR) calcium leak has been described in ARVC where it has been shown to be related to mutations of the ryanodine receptor [96]. SR calcium leak was also described in failing RV myocytes of pulmonary hypertensive rats but the underlying mechanisms were different and involved a SR calcium overload likely to be related to (i) an increased calcium entry due to the APD prolongation and (ii) a decreased sodium/calcium exchanger function [82]. In the latter study calcium transient alternans was commonly observed at high pacing rates (9 Hz). This may contribute to or result from electrical alternans observed *in vivo* and *ex vivo* in these failing animals (Fig. 6).

The specific shape and thickness of the RV make it sensitive to changes in diastolic volume and the failing RV is typically dilated and thus exposed to a greater level of stretch than its left counterpart. RV stretch consecutive to chronic pulmonary regurgitation has been shown to contribute to arrhythmia generation by decreasing APD (unlike the APD increase commonly observed in models of pulmonary hypertension), increasing APD dispersion and slowing conduction velocity [97] via the activation of mechanosensitive channels (see [98] for review). In patients with repaired TOF, a good correlation has been found between RV dilatation, QRS duration and the incidence of ventricular tachycardia [99] and RV mechanical dispersion was increased in ARVC patients presenting with life-threatening arrhythmias [100].

9. Conclusion

The cellular and extracellular remodeling occurring during heart failure set the stage, alone or in combination, stage for life-threatening

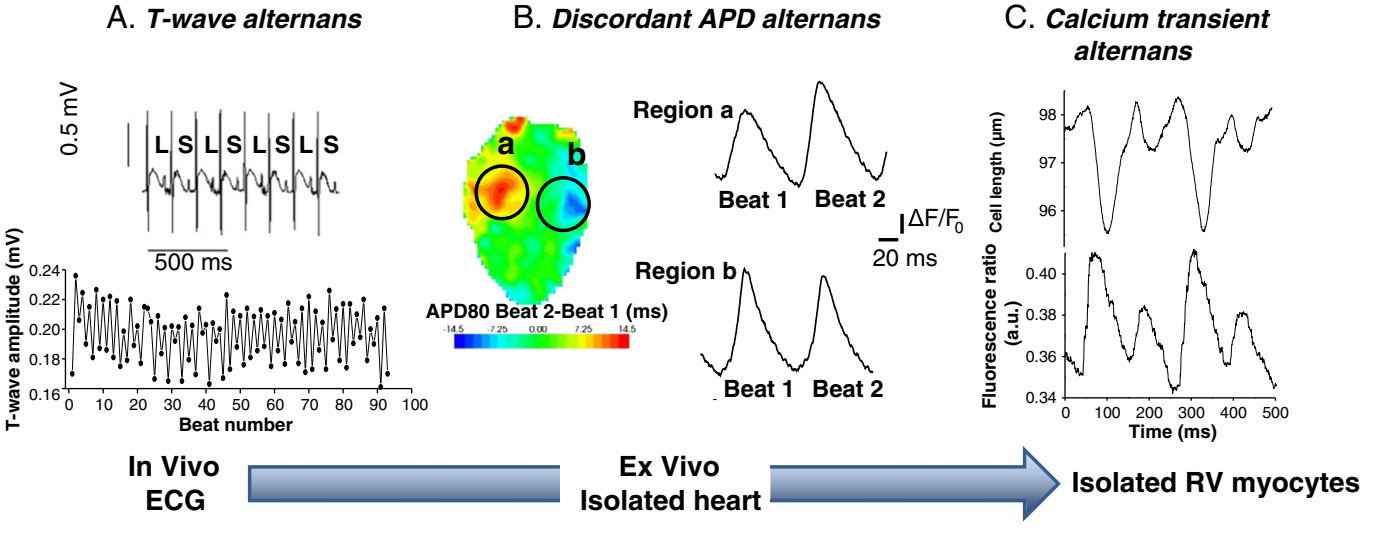


Fig. 6. T-wave alternans of the *in vivo* ECG in the failing RV of pulmonary hypertensive rats, manifested as discordant APD alternans in Langendorff-perfused hearts and calcium transient alternans in isolated RV myocytes. A. ECG trace (top) from a rat with RV failure and a graph of the beat by beat T-wave amplitude (bottom) showing T-wave amplitude alternans over 93 consecutive beats. T-wave alternans was observed in a proportion of failing rats in which they represented more than 9% of the analyzed beats. B. Map of APD80 difference over two consecutive beats showing discordant APD alternans between region a and b (see traces for each region). 67% of failing hearts but no control hearts ($P < 0.05$) showed RV discordant APD alternans when electrically stimulated above 10 Hz. C. Traces showing simultaneous cell shortening and calcium transient alternans in a failing RV myocyte paced at 9 Hz. A majority of isolated failing RV myocytes displayed alternans when paced at 9 Hz, control cells did not ($P < 0.001$). Reproduced and modified with permission from cu.

arrhythmias. Reentrant as well as triggered arrhythmias of different types may ensue, each of which requires a different therapeutic approach. The identification of the primary arrhythmia mechanism in each individual heart failure patient and of the matched therapeutic approach poses a challenge to clinical cardiology.

References

[1] G.F. Tomaselli, D.P. Zipes, What causes sudden death in heart failure? Circ. Res. 95 (2004) 754–763.
[2] E. Braunwald, Heart Disease. A Textbook of Cardiovascular Medicine, W. B. Saunders, Philadelphia, 1997.
[3] R. Coronel, J.J. van Lieshout, J.R. de Groot, Defining heart failure, Cardiovasc. Res. 50–3 (2001) 419–422.
[4] S.J. Connolly, P. Dorian, R.S. Roberts, M. Gent, S. Bailin, E.S. Fain, K. Thorpe, J. Champagne, M. Talajic, B. Coutu, G.C. Gronefeld, S.H. Hohnloser, Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial, JAMA 295 (2006) 165–171.
[5] S. Nakahara, R. Tung, R.J. Ramirez, Y. Michowitz, M. Vaseghi, E. Buch, J. Gima, I. Wiener, A. Mahajan, N.G. Boyle, K. Shivkumar, Characterization of the arrhythmogenic substrate in ischemic and nonischemic cardiomyopathy implications for catheter ablation of hemodynamically unstable ventricular tachycardia, J. Am. Coll. Cardiol. 55 (2010) 2355–2365.
[6] M.J. Janse, F.J.L. Van Capelle, H. Morsink, A.G. Kléber, F. Wilms-Schopman, R. Cardinal, C. Naumann d'Alnoncourt, D. Durrer, Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Evidence for two different arrhythmogenic mechanisms, Circ. Res. 47 (1980) 151–165.
[7] S.M. Pogwizd, Nonreentrant mechanisms underlying spontaneous ventricular arrhythmias in a model of nonischemic heart failure in rabbits, Circulation 92 (1995) 1034–1048.
[8] J.T. Vermeulen, M.A. McGuire, T. Opthof, R. Coronel, J.M.T. De Bakker, C. Kloepping, M.J. Janse, Triggered activity and automaticity in ventricular trabeculae of failing human and rabbit hearts, Cardiovasc. Res. 28 (1994) 1547–1554.
[9] Z.F. Issa, J. Rosenberger, W.J. Groh, J.M. Miller, D.P. Zipes, Ischemic ventricular arrhythmias during heart failure: a canine model to replicate clinical events, Hear. Rhythm. 2 (2005) 979–983.
[10] R.J. van Oort, A. Garbino, W. Wang, S.S. Dixit, A.P. Landstrom, N. Gaur, A.C. De Almeida, D.G. Skapura, Y. Rudy, A.R. Burns, M.J. Ackerman, X.H.T. Wehrens, Disrupted junctional membrane complexes and hyperactive ryanodine receptors after acute junctophilin knockdown in mice/clinical perspective, Circulation 123 (2011) 979–988.
[11] T. van der Bom, B.J. Bouma, F.J. Meijboom, A.H. Zwinderman, B.J.M. Mulder, The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation, Am. Heart J. 164 (2012) 568–575.
[12] S. Richard, F. Leclercq, S.p. Lemaire, C. Piot, J.l. Nargeot, Ca^{2+} currents in compensated hypertrophy and heart failure, Cardiovasc. Res. 37 (1998) 300–311.
[13] T. Aiba, G. Tomaselli, Electrical remodeling in dyssynchrony and resynchronization, J. Cardiovasc. Trans. Res. 5 (2012) 170–179.
[14] M.J. Janse, J.T. Vermeulen, T. Opthof, R. Coronel, F.J.G. Wilms-Schopman, H.M.E. Rademaker, A. Baartscheer, L.R.C. Dekker, Arrhythmogenesis in heart failure, J. Cardiovasc. Electrophysiol. 12 (2001) 496–499.
[15] D.M. Roden, Taking the "idio" out of "idiosyncratic": predicting torsades de pointes, Pacing Clin. Electrophysiol. 21 (1998) 1029–1034.
[16] M.R. Franz, R. Cima, D. Wang, D. Profitt, R. Kurz, Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias, Circulation 86 (1992) 968–978.
[17] O. Kinoshita, T. Tomita, T. Hanaoka, H. Tsutsui, H. Imamura, Y. Yazaki, N. Watanabe, M. Hongo, K. Kubo, T-wave alternans in patients with right ventricular tachycardia, Cardiology 100 (2003) 86–92.
[18] M.J. Janse, A.G. Kléber, E. Downar, D. Durrer, Changements electrophysiologiques pendant l'ischemie myocardique et mecanisme possible des troubles du rythme ventriculaire, Ann. Cardiol. Angeiol. 26 (1977) 551–554.
[19] C.E. Jackson, R.C. Myles, I.K. Tsorlalis, J.R. Dalzell, R.J. Spooner, J.R. Rodgers, V. Bezlyak, N. Greenlaw, I. Ford, S.M. Cobbe, M.C. Petrie, J.J.V. McMurray, Profile of microvolt T-wave alternans testing in 1003 patients hospitalized with heart failure, Eur. J. Hear. Fail. 14 (2012) 377–386.
[20] G. Michael, L. Xiao, X.Y. Qi, D. Dobrev, S. Nattel, Remodelling of cardiac repolarization: how homeostatic responses can lead to arrhythmogenesis, Cardiovasc. Res. 81 (2009) 491–499.
[21] S. Nattel, A. Maguy, S. Le Bouter, Y.H. Yeh, Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation, Physiol. Rev. 87 (2007) 425–456.
[22] J. Pu, P.A. Boyden, Alterations of Na^+ currents in myocytes from epicardial border zone of the infarcted heart: a possible ionic mechanism for reduced excitability and postrepolarization refractoriness, Circ. Res. 81 (1997) 110–119.
[23] S.M. Pogwizd, R.H. Hoyt, J.E. Saffitz, P.B. Corr, J.L. Cox, M.E. Cain, Reentrant and focal mechanisms underlying ventricular tachycardia in the human heart, Circulation 86 (1992) 1872–1887.
[24] D.J. Pinsky, E.S. Sciacca, J.S. Steinberg, QT dispersion as a marker of risk in patients awaiting heart transplantation, J. Am. Coll. Cardiol. 29 (1997) 1576–1584.
[25] G.R. Mines, On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation, Trans. R. Soc. Can. Sect. IV (1914) 43–53.
[26] J. Han, G.K. Moe, Nonuniform recovery of excitability in ventricular muscle, Circ. Res. 14 (1964) 44–61.
[27] R. Coronel, F.J.G. Wilms-Schopman, T. Opthof, M.J. Janse, Dispersion of repolarization and arrhythmogenesis, Hear. Rhythm. 6 (2009) 537–543.
[28] R. Coronel, F.J. Wilms-Schopman, M.J. Janse, Anti- or profibrillatory effects of Na^+ channel blockade depend on the site of application relative to gradients in repolarization, Front. Card. Electrophysiol. 1 (2011) 10.
[29] R.F. Wiegerinck, A.A. van Veen, C.N. Belterman, C.A. Schumacher, M. Noorman, J.M. de Bakker, R. Coronel, Transmural dispersion of refractoriness and conduction velocity is associated with heterogeneously reduced connexin43 in a rabbit model of heart failure, Hear. Rhythm. 5 (2008) 1178–1185.
[30] X. Ai, S.M. Pogwizd, Connexin 43 downregulation and dephosphorylation in nonischemic heart failure is associated with enhanced colocalized protein phosphatase type 2A, Circ. Res. 96 (2005) 54–63.
[31] N.J. Severs, A.F. Bruce, E. Dupont, S. Rothery, Remodelling of gap junctions and connexin expression in diseased myocardium, Cardiovasc. Res. 80 (2008) 9–19.
[32] J.A. Jansen, M. Noorman, H. Musa, M. Stein, S. de Jong, R. van der Nagel, T.J. Hund, P.J. Mohler, M.A. Vos, T.A. van Veen, J.M. de Bakker, M. Delmar, H.V. van Rijen, Reduced heterogeneous expression of Cx43 results in decreased Nav1.5 expression and reduced sodium current that accounts for arrhythmia vulnerability in conditional Cx43 knockout mice, Hear. Rhythm. 9 (2012) 600–607.
[33] M. Stein, T.A.B. van Veen, R.N.W. Hauer, J.M.T. de Bakker, H.V.M. van Rijen, A 50% reduction of excitability but not of intercellular coupling affects conduction velocity restitution and activation delay in the mouse heart, PLoS One 6 (2011) e20310.
[34] H.J. Jongsma, R. Wilders, Gap junctions in cardiovascular disease, Circ. Res. 86 (2000) 1193–1197.
[35] R. Wilders, Arrhythmogenic right ventricular cardiomyopathy: considerations from *in silico* experiments, Front. Physiol. 3 (2012) 168.
[36] R.F. Wiegerinck, A.O. Verkerk, C.N. Belterman, T.A.B. Van Veen, A. Baartscheer, T. Opthof, R. Wilders, J.M.T. de Bakker, R. Coronel, Larger cell size in rabbits with heart failure increases myocardial conduction velocity and QRS duration, Circulation 113 (2006) 806–813.
[37] A. Shiroshita-Takeshita, M. Sakabe, K. Haugan, J.K. Hennan, S. Nattel, Model-dependent effects of the gap junction conduction-enhancing antiarrhythmic peptide rotigaptide (ZP123) on experimental atrial fibrillation in dogs, Circulation 115 (2007) 310–318.
[38] R.F. Wiegerinck, J.M.T. De Bakker, T. Opthof, N. de Jonge, H. Kirkels, F.J.G. Wilms-Schopman, R. Coronel, The effect of enhanced gap junctional conductance on ventricular conduction in explanted hearts from patients with heart failure, Basic Res. Cardiol. 104 (2009) 321–332.
[39] M. Delmar, Connexin43 regulates sodium current; ankyrin-G modulates gap junctions: the intercalated disc exchanger, Cardiovasc. Res. 93 (2012) 220–222.
[40] H.M. den Ruijter, A.O. Verkerk, C.A. Schumacher, S.M. Houten, C.N.W. Belterman, A. Baartscheer, I.A. Brouwer, M. van Bilsen, B. de Roos, R. Coronel, A diet rich in unsaturated fatty acids prevents progression toward heart failure in a rabbit model of pressure and volume overload/clinical perspective, Circ. Heart Fail. 5 (2012) 376–384.
[41] K. Gima, Y. Rudy, Ionic current basis of electrocardiographic waveforms: a model study, Circ. Res. 90 (2002) 889–896.
[42] A. Baartscheer, C.A. Schumacher, C.N.W. Belterman, R. Coronel, J.W.T. Fiolet, SR calcium handling and calcium after-transients in a rabbit model of heart failure, Cardiovasc. Res. 58 (2003) 99–108.
[43] D.M. Bers, Calcium cycling and signaling in cardiac myocytes, Annu. Rev. Physiol. 70 (2008) 23–49.
[44] A.M. Gomez, H.H. Valdivia, H. Cheng, M.R. Lederer, L.F. Santana, M.B. Cannell, S.A. McCune, R.A. Altschuld, W.J. Lederer, Defective excitation–contraction coupling in experimental cardiac hypertrophy and heart failure, Science 276 (1997) 800–806.
[45] E.J. Griffiths, D. Balaska, W.H.Y. Cheng, The ups and downs of mitochondrial calcium signalling in the heart, Biochim. Biophys. Acta Bioenerg. 1797 (2010) 856–864.
[46] K.T. Weber, C.G. Brilla, S.E. Campbell, E. Guarda, G. Zhou, K. Sriram, Myocardial fibrosis: role of angiotensin II and aldosterone. [Review] [74 refs], Basic Res. Cardiol. 88 (Suppl. 1) (1993) 107–124.
[47] K.T. Weber, C.G. Brilla, J.S. Janicki, Myocardial fibrosis: functional significance and regulatory factors. [Review] [116 refs], Cardiovasc. Res. 27 (1993) 341–348.
[48] M. Boulaksil, S.K.G. Winckels, M.A. Engelen, M. Stein, T.A.B. van Veen, J.A. Jansen, A.C. Linnenbank, M.F.A. Bierhuizen, W.A. Groenewegen, M.F.M. van Oosterhout, J.H. Kirkels, N. de Jonge, A. Varr, M.A. Vos, J.M.T. de Bakker, H.V.M. van Rijen, Heterogeneous Connexin43 distribution in heart failure is associated with dispersed conduction and enhanced susceptibility to ventricular arrhythmias, Eur. J. Hear. Fail. 12 (2010) 913–921.
[49] R. Wilders, M.B. Wagner, D. Golod, R. Kumar, Y.-G. Wang, W.N. Goolsby, R.W. Joyner, H.J. Jongsma, Effects of anisotropy on the development of cardiac arrhythmias associated with focal activity, Pfluegers Arch. 441 (2000) 301–312.
[50] M.G. Hoogendijk, M. Potse, A. Vinet, J.M. de Bakker, R. Coronel, ST segment elevation by current-to-load mismatch: an experimental and computational study, Hear. Rhythm. 8 (2011) 111–118.
[51] M.G. Hoogendijk, T. Opthof, P.G. Postema, A.A. Wilde, J.M. de Bakker, R. Coronel, The Brugada ECG pattern: a marker of channelopathy, structural heart disease, or neither? Toward a unifying mechanism of the Brugada syndrome, Circ. Arrhythm. Electrophysiol. 3 (2010) 283–290.
[52] M.S. Spach, W.T. Miller, D.B. Geselowitz, R.C. Barr, J.M. Kootsey, E.A. Johnson, The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect the membrane currents, Circ. Res. 48 (1981) 39–54.

[53] J.M. de Bakker, F.J. van Capelle, M.J. Janse, S. Tasseron, J.T. Vermeulen, N. de Jonge, J.R. Lahpor, Slow conduction in the infarcted human heart. 'Zigzag' course of activation, Circulation 88 (1993) 915–926.
[54] R.C. Saumarez, A.K.B. Slade, A.A. Grace, N. Sadoul, A.J. Camm, W.J. Mckenna, The significance of paced electrgram fractionation in hypertrophic cardiomyopathy, Circulation 91 (1995) 2762–2768.
[55] T. Kawara, R. Derksen, J.R. de Groot, R. Coronel, S. Tasseron, A.C. Linnenbank, R.N.W. Hauer, H. Kirkels, M.J. Janse, J.M.T. De Bakker, Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis, Circulation 104 (2001) 3069–3075.
[56] J.M. Davidenko, A.V. Pertsov, R. Salomonsz, W. Baxter, J. Jalife, Stationary and drifting spiral waves of excitation in isolated cardiac muscle, Nature 355 (1992) 349–351.
[57] F.H. Samie, J. Jalife, Mechanisms underlying ventricular tachycardia and its transition to ventricular fibrillation in the structurally normal heart, Cardiovasc. Res. 50 (2001) 242–250.
[58] P. Coumel, The management of clinical arrhythmias. An overview on invasive versus non-invasive electrophysiology, Eur. Heart J. 8 (1987) 92–99.
[59] C.M. Tracy, J. Winkler, E. Brittain, M.B. Leon, S.E. Epstein, R.O. Bonow, Determinants of ventricular arrhythmias in mildly symptomatic patients with coronary artery disease and influence of inducible left ventricular dysfunction on arrhythmia frequency, JACC 9 (1978) 483–488.
[60] D.E. Hansen, C.S. Craig, L.M. Hondeghem, Stretch-induced arrhythmias in the isolated canine ventricle. Evidence for the importance of mechanoelectrical feedback, Circulation 81 (1990) 1094–1105.
[61] Z. Wang, K. Taylor, W.D. Denney, D.E. Hansen, Initiation of ventricular extrasystoles by myocardial stretch in chronically dilated and failing canine left ventricle, Circulation 90 (1994) 2022–2031.
[62] A. Kamkin, I. Kiseleva, G. Isenberg, Stretch-activated currents in ventricular myocytes: amplitude and arrhythmogenic effects increase with hypertrophy, Cardiovasc. Res. 48 (2000) 402–408.
[63] T. Opthof, P. Sutton, R. Coronel, S. Wright, P. Kallis, P. Taggart, The association of abnormal ventricular wall motion and increased dispersion of repolarization in humans is independent of the presence of myocardial infarction, Front. Physiol. 3 (2012).
[64] R. Marchioli, C. Schweiger, L. Tavazzi, F. Valagussa, Efficacy of n-polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial, Lipids 36 (2001) S119–S126.
[65] H.M. Den Ruijter, G. Berecki, T. Opthof, A.O. Verkerk, P.L. Zock, R. Coronel, Pro- and antiarrhythmic properties of a diet rich in fish oil, Cardiovasc. Res. 73 (2007) 316–325.
[66] G.E. Billman, J.X. Kang, A. Leaf, Prevention of sudden death by dietary pure n-3 polyunsaturated fatty acids in dogs, Circulation 99 (1999) 2452–2457.
[67] A.O. Verkerk, A.C.G. van Ginneken, G. Berecki, H.M. den Ruijter, C.A. Schumacher, M.W. Veldkamp, A. Baartscheer, S. Casini, T. Opthof, R. Hovenier, J.W.T. Fiolet, P.L. Zock, R. Coronel, Incorporated sarcolemmal fish oil fatty acids shorten pig ventricular action potentials, Cardiovasc. Res. 70 (2006) 509–520.
[68] H.M. den Ruijter, G. Berecki, A.O. Verkerk, D. Bakker, A. Baartscheer, C.A. Schumacher, C.N.W. Belterman, N. de Jonge, J.W.T. Fiolet, I.A. Brouwer, R. Coronel, Acute administration of fish oil inhibits triggered activity in isolated myocytes from rabbits and patients with heart failure, Circulation 117 (2008) 536–544.
[69] M.H. Raitt, W.E. Connor, C. Morris, J. Kron, B. Halperin, S. Chugh, J. McClelland, J. Cook, K. MacMurdy, R. Swenson, S.L. Connor, G. Gerhard, D.F. Kraemer, D. Oscran, C. Marchant, D. Calhoun, R. Shriner, J. McAnulty, Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators, JAMA 293 (2005) 2884–2891.
[70] R. Coronel, F.J. Wilms-Schopman, H.M. Den Ruijter, C.N. Belterman, C.A. Schumacher, T. Opthof, R. Hovenier, A.G. Lemmens, A.H. Terpstra, M.B. Katan, P. Zock, Dietary n-3 fatty acids promote arrhythmias during acute regional myocardial ischemia in isolated pig hearts, Cardiovasc. Res. 73 (2006) 386–394.
[71] Q. Chen, L.-Q. Cheng, T.-H. Xiao, Y.-X. Zhang, M. Zhu, R. Zhang, K. Li, Y. Wang, Y. Li, Effects of omega-3 fatty acid for sudden cardiac death prevention in patients with cardiovascular disease: a contemporary meta-analysis of randomized, controlled trials, Cardiovasc. Drugs Ther. 25 (2011) 259–265.
[72] Q. Lou, D.L. Janks, K.M. Holzem, D. Lang, B. Onal, C.M. Ambrosi, V.V. Fedorov, I.W. Wang, I.R. Efimov, Right ventricular arrhythmogenesis in failing human heart: the role of conduction and repolarization remodeling, Am. J. Physiol. Heart Circ. Physiol. 303 (2012) H1426–H1434.
[73] D.P. Zipes, A.J. Camm, M. Borggrefe, A.E. Buxton, B. Chaitman, M. Fromer, G. Gregoratos, G. Klein, A.J. Moss, R.J. Myerburg, S.G. Priori, M.A. Quinones, D.M. Roden, M.J. Silka, C. Tracy, S.C. Smith Jr., A.K. Jacobs, C.D. Adams, E.M. Antman, J.L. Anderson, S.A. Hunt, J.L. Halperin, R. Nishimura, J.P. Ornato, R.L. Page, B. Riegel, J.J. Blanc, A. Budaj, V. Dean, J.W. Deckers, C. Despres, K. Dickstein, J. Lekakis, K. McGregor, M. Metra, J. Morais, A. Osterspey, J.L. Tamargo, J.L. Zamorano, ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society, Circulation 114 (2006) e385–e484.
[74] V. Lambert, A. Capderou, B.E. Le, C. Rucker-Martin, E. Deroubaix, E. Gouadon, N. Raymond, B. Stos, A. Serraf, J.F. Renaud, Right ventricular failure secondary to chronic overload in congenital heart disease: an experimental model for therapeutic innovation, J. Thorac. Cardiovasc. Surg. 139 (2010) 1197–1204.
[75] J.K. Lee, I. Kodama, H. Honjo, T. Anno, K. Kamiya, J. Toyama, Stage-dependent changes in membrane currents in rats with monocrotaline-induced right ventricular hypertrophy, Am. J. Physiol. 272 (1997) H2833–H2842.
[76] D. Benoist, R. Stones, M. Drinkhill, O. Bernus, E. White, Arrhythmogenic substrate in hearts of rats with monocrotaline-induced pulmonary hypertension and right ventricular hypertrophy, Am. J. Physiol. Heart Circ. Physiol. 300 (2011) H2230–H2237.
[77] P. Turrini, D. Corrado, C. Basso, A. Nava, B. Bauce, G. Thiene, Dispersion of ventricular depolarization–repolarization: a noninvasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy, Circulation 103 (2001) 3075–3080.
[78] W.A. Helbing, A.A. Roest, R.A. Niezen, H.W. Vliegen, M.G. Hazekamp, J. Ottenkamp, R.A. de, E.E. Van der Wall, ECG predictors of ventricular arrhythmias and biventricular size and wall mass in tetralogy of Fallot with pulmonary regurgitation, Heart 88 (2002) 515–519.
[79] Z. Hong-Liang, L. Qin, L. Zhi-Hong, Z. Zhi-hui, X. Chang-Ming, N. Xin-Hai, H. Jian-guo, W. Ying-jie, Z. Shu, Heart rate-corrected QT interval and QT dispersion in patients with pulmonary hypertension, Wien. Klin. Wochenschr. 121 (2009) 330–333.
[80] M. Hardziyenka, M.E. Campian, A.O. Verkerk, S. Surie, A.C. van Ginneken, S. Hakim, A.C. Linnenbank, H.A. de Bruin-Bon, L. Beekman, M.N. van der Plas, C.A. Remme, T.A. van Veen, P. Bresser, J.M. de Bakker, H.L. Tan, Electrophysiologic remodeling of the left ventricle in pressure overload-induced right ventricular failure, J. Am. Coll. Cardiol. 59 (2012) 2193–2202.
[81] S. Umar, J.H. Lee, L.E. de, A. Iorga, R. Partow-Navid, A. Bapat, A. van der Laarse, R. Saggar, R. Saggar, D.L. Ypey, H.S. Karagueuzian, M. Eghbali, Spontaneous ventricular fibrillation in right ventricular failure secondary to chronic pulmonary hypertension, Circ. Arrhythm. Electrophysiol. 5 (2012) 181–190.
[82] D. Benoist, R. Stones, M.J. Drinkhill, A.P. Benson, Z. Yang, C. Cassan, S.H. Gilbert, D.A. Saint, O. Cazorla, D.S. Steele, O. Bernus, E. White, Cardiac arrhythmia mechanisms in rats with heart failure induced by pulmonary hypertension, Am. J. Physiol. Heart Circ. Physiol. 302 (2012) H2381–H2395.
[83] M. Uzzaman, H. Honjo, Y. Takagishi, L. Emdad, A.I. Magee, N.J. Severs, I. Kodama, Remodeling of gap junctional coupling in hypertrophied right ventricles of rats with monocrotaline-induced pulmonary hypertension, Circ. Res. 86 (2000) 871–878.
[84] S.R. Kaplan, J.J. Gard, N. Protonotarios, A. Tsatsopoulou, C. Spiliopoulou, A. Anastasakis, C.P. Squarcioni, W.J. Mckenna, G. Thiene, C. Basso, N. Brousse, G. Fontaine, J.E. Saffitz, Remodeling of myocyte gap junctions in arrhythmogenic right ventricular cardiomyopathy due to a deletion in plakoglobin (Naxos disease), Hear. Rhythm. 1 (2004) 3–11.
[85] M. Cerrone, M. Noorman, X. Lin, H. Chkourko, F.X. Liang, R. van der Nagel, T. Hund, W. Birchmeier, P. Mohler, T.A. van Veen, H.V. van Rijen, M. Delmar, Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency, Cardiovasc. Res. 95 (2012) 460–468.
[86] A.P. Lourenco, R. Roncon-Albuquerque Jr., C. Bras-Silva, B. Faria, J. Wieland, T. Henriques-Coelho, J. Correia-Pinto, A.F. Leite-Moreira, Myocardial dysfunction and neurohumoral activation without remodeling in left ventricle of monocrotaline-induced pulmonary hypertensive rats, Am. J. Physiol. Heart Circ. Physiol. 291 (2006) H1587–H1594.
[87] M.P. Marra, L. Leoni, B. Bauce, F. Corbetti, A. Zorzi, F. Migliore, M. Silvano, I. Rigato, F. Tona, G. Tarantini, L. Cacciavillani, C. Basso, G. Buja, G. Thiene, S. Iliceto, D. Corrado, Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance, Circ. Arrhythm. Electrophysiol. 5 (2012) 91–100.
[88] K. Zeppenfeld, M.J. Schalij, M.M. Bartelings, U.B. Tedrow, B.A. Koplan, K. Soejima, W.G. Stevenson, Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus, Circulation 116 (2007) 2241–2252.
[89] M. Vogel, J. Sponring, S. Cullen, J.E. Deanfield, A.N. Redington, Regional wall motion and abnormalities of electrical depolarization and repolarization in patients after surgical repair of tetralogy of Fallot, Circulation 103 (2001) 1669–1673.
[90] A.K. Steriotis, B. Bauce, L. Daliento, I. Rigato, E. Mazzotti, A.F. Folino, M.P. Marra, L. Brugnaro, A. Nava, Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy, Am. J. Cardiol. 103 (2009) 1302–1308.
[91] J.B. Thambo, G.M. De, O. Xhaet, P.D. Santos, F. Roubertie, L. Labrousse, X. Iriart, S. Ploux, M. Haissaguerre, P. Bordachar, Biventricular pacing in patients with Tetralogy of Fallot: non-invasive epicardial mapping and clinical impact, Int. J. Cardiol. 163 (2) (2013 Feb 20) 170–174, http://dx.doi.org/10.1016/j.ijcard.2011.06.005, Epub 2011 Jul 31.
[92] L.F. Tops, K. Prakasa, H. Tandri, D. Dalal, R. Jain, V.L. Dimaano, D. Dombroski, C. James, C. Tichnell, A. Daly, F. Marcus, M.J. Schalij, J.J. Bax, D. Bluemke, H. Calkins, T.P. Abraham, Prevalence and pathophysiologic attributes of ventricular dyssynchrony in arrhythmogenic right ventricular dysplasia/cardiomyopathy, J. Am. Coll. Cardiol. 54 (2009) 445–451.
[93] N. Shanmugam, J. Yap, R.S. Tan, T.T. Le, F. Gao, J.X. Chan, D. Chong, K.L. Ho, B.Y. Tan, C.K. Ching, W.S. Teo, J.L. Tan, R. Liew, Fragmented QRS complexes predict right ventricular dysfunction and outflow tract aneurysms in patients with repaired tetralogy of Fallot, Int. J. Cardiol. (2012 Apr 20), Epub ahead of print.
[94] S. Peters, M. Truemmel, B. Koehler, Prognostic value of QRS fragmentation in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia, J. Cardiovasc. Med. (Hagerstown) 13 (2012) 295–298.
[95] M.M. Cheung, R.G. Weintraub, R.J. Cohen, T.R. Karl, J.L. Wilkinson, A.M. Davis, T wave alternans threshold late after repair of tetralogy of Fallot, J. Cardiovasc. Electrophysiol. 13 (2002) 657–661.

[96] N. Tiso, D.A. Stephan, A. Nava, A. Bagattin, J.M. Devaney, F. Stanchi, G. Larderet, B. Brahmbhatt, K. Brown, B. Bauce, M. Muriago, C. Basso, G. Thiene, G.A. Danieli, A. Rampazzo, Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2), Hum. Mol. Genet. 10 (2001) 189–194.
[97] R. Gray, G. Greve, R. Chen, C. Fry, D. Barron, M.J. Lab, P.A. White, A.N. Redington, D.J. Penny, Right ventricular myocardial responses to chronic pulmonary regurgitation in lambs: disturbances of activation and conduction, Pediatr. Res. 54 (2003) 529–535.
[98] E. White, Mechanosensitive channels: therapeutic targets in the myocardium? Curr. Pharm. Des. 12 (2006) 3645–3663.
[99] M.A. Gatzoulis, J.A. Till, J. Somerville, A.N. Redington, Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death, Circulation 92 (1995) 231–237.
[100] S.I. Sarvari, K.H. Haugaa, O.G. Anfinsen, T.P. Leren, O.A. Smiseth, E. Kongsgaard, J.P. Amlie, T. Edvardsen, Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction, Eur. Heart J. 32 (2011) 1089–1096.
[101] A.O. Verkerk, A. Baartscheer, J.R. de Groot, R. Wilders, R. Coronel, Etiology-dependency of ionic remodeling in cardiomyopathic rabbits, Int. J. Cardiol. 148 (2011) 154–160.